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3 SUMMARY OF SAFETY AND EFFECTIVENESS DATA

3.1 INDICATION FOR USE

SCULPTRA™ is intended to correct shape and contour deficiencies resulting from facial fat loss (lipoatrophy) in people with human immunodeficiency virus.

3.2 DEVICE DESCRIPTION

SCULPTRA is provided in a vial as a sterile lyophilisate consisting of mannitol, sodium carboxymethylcellulose, and poly-L-lactic acid (PLLA) (see Table 3-1). Before use, the lyophilisate is reconstituted with 3 mL of sterile water for injection, USP (SWFI), which is provided by the end-user.

TABLE 3-1 COMPOSITION OF LYOPHILISATE OF SCULPTRA

Each vial o⬛phllisate contains		
Component	Composition of Lyophilisate (%)	Concentration after Reconstitution with 3 mL SWFI (%)
PLLA	⬛	⬛
Sodium Carboxymethylcellulose		
Mannitol		
Sterile Water for Injection		
Total	100	100

Abbreviations: N/A = not applicable; PLLA = poly-L-lactic acid

3.3 ALTERNATIVE PRACTICES AND PROCEDURES

Although there are no marketed products in the US specifically approved for correction of the signs of facial fat loss in patients with lipoatrophy, there are products that can be used. These products fall into two categories: bio-absorbable fillers and permanent implants.

Bio-absorbable products currently marketed in the US, which have a short duration following injection for use in soft-tissue, include:

- Bovine collagen (Zyplast®)
- Human collagen (Cosmoderm®, CosmoPlast®)
- Dermal cadaveric tissue (Cymetra®, Alloderm®)
- Human particulate fascia lata (Fascian®)

Permanent options include expanded polytetrafluoro-ethylene (ePTFE) marketed as Softform®, and Gore Tex® implants.

The advantages and disadvantages of various injectable products used to correct dermal depressions are related to the product composition and resorbability. Non-permanent fillers may require frequent re-application. Fillers from animal sources such as bovine collagen can cause

allergic reactions. Permanent implants do not address the more subtle facial contour distortions that may be seen with facial lipoatrophy.

Other treatment options include:

- Body fat cell transplants; if transplanted, the fat is exposed to the same environment that led to the lipoatrophy, thus the transplanted fat disappears. Transplantable fat cells of HIV lipoatrophy patients are already damaged. Furthermore, the transferred fat may be absorbed quickly by the body resulting in an effect that is not long lasting, so additional procedures may be required. This is a surgical procedure requiring healing of donor and recipient site.

- *Facelift; may improve appearance for mild cases without addressing the volume defect.* But, this is a complicated and expensive surgical procedure and requires long periods of time for healing.

There is an unmet need in the US, since there are no approved medical products in the US *specifically indicated for the treatment of facial fat loss in patients with lipoatrophy.* Those products that are used have limitations relative to safety, durability and price. The lipoatrophy patient is in great need of a product that provides effective, long-lasting, safe and affordable treatment to help them improve their physical appearance and restore their self-image.

3.4 MARKETING HISTORY

SCULPTRA (injectable poly-L-lactic acid) was developed in Europe and marketed under the trade name NEW-FILL®, with CE Mark certification obtained in November 1999 as a class III device under the category "Wrinkles Filling Product." The product was initially developed by Biotech Industries S.A. Luxembourg, and was acquired by Dermik Laboratories (Dermik) effective May 2002.

NEW-FILL is marketed in the following countries: Argentina, Australia, Brazil, Bulgaria, European Union countries (Austria, Belgium/Luxembourg/Netherlands, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Portugal, Spain, Sweden, United Kingdom), Hungary, Israel, Lebanon, Malaysia, Mexico, Morocco, Norway, Poland, Romania, Russia, Saudi Arabia, South Africa, Switzerland, and the United Arab Emirates. At present, the SCULPTRA tradename is not used outside the US.

NEW-FILL has not been withdrawn from any marketplace for any reason related to the safety and effectiveness of the device.

3.5 POTENTIAL ADVERSE EVENTS

Based upon data obtained through clinical studies, the known treatment-related risks for the use of SCULPTRA include immediate and transient injection-related events such as bleeding from the injection site, injection site tenderness or discomfort, injection site erythema or inflammation, bruising (hematoma), and injection site edema (swelling). Delayed events may include the formation of nodules or induration.

In the pivotal clinical studies, the most commonly observed adverse effect in the correction of facial fat loss (lipoatrophy) was the delayed occurrence of injection site nodules. Nodules were confined to the injection site and were typically non-visible, asymptomatic, small, but palpable. Nodules tended to occur within the first six months to one year after initial injection, and in some cases resolved spontaneously without specific treatment. A summary of the adverse events seen in the pivotal studies is shown in Section 3.7.1, Table 3-9.

The following potential adverse events were reported at least once from additional sources of safety information and may also be associated with the use of SCULPTRA; however, these events were not observed in the pivotal clinical studies: nodules with inflammation or dyspigmentation, fever, malaise, injection site abscess, allergic reaction, dermatomyositis, injection site atrophy, face edema, Quincke's edema, injection site fat atrophy, photosensitive reaction, fatigue, injection site granuloma, hypersensitivity reaction.

NEW-FILL (SCULPTRA) is a well-tolerated treatment for the correction of the signs of facial fat loss in patients with lipoatrophy with adverse effects typically limited to localized injection site events.

3.6   SUMMARY OF NONCLINICAL STUDIES

3.6.1   Toxicology Summary

The biocompatibility studies comprising this nonclinical safety assessment complied with the International Standard ISO 10993-1 Biological Evaluation of Medical Devices. SCULPTRA is considered to be an implant device in permanent (>30 days) contact with tissue/bone. The safety assessment studies completed for this device included: cytotoxicity, sensitization, irritation, systemic toxicity, sub-chronic toxicity, genotoxicity, implantation, hemocompatibility, and pyrogenicity studies. Table 3-2 below summarizes the results of these studies.

TABLE 3-2	NONCLINICAL TOXICITY STUDIES OF THE DEVICE PERFORMED IN ACCORDANCE WITH ISO 10993 GUIDELINES
TEST CATEGORY	**STUDY RESULTS**
Cytotoxicity	Device was not cytotoxic.
Sensitization	Device was not a sensitizer.
Irritation or Intracutaneous toxicity	Device was considered to be a weak irritant under the conditions of this study.
Systemic Toxicity (Acute)	No signs of toxicity were observed with a single intraperitoneal injection of 5000 mg/Kg in mice.
Sub-chronic Toxicity	The device was well tolerated (locally and systemically) over a 90-Day exposure period when administered by the intradermal route with 3 injections of 0.2 mL/rat on Days 0, 21 and 42.
Genotoxicity	Device and Device Extract were not mutagenic, nor clastogenic, in the presence or in the absence of metabolic activation.
Implantation (Local Tolerance)	No notable specific lesions were observed with the placebo, or the 0.2 mL injections. A foreign body granulomatous inflammation developed at the periphery of the 1.0 mL injection sites.
Hemocompatibility	Device did not induce *in vitro* human complement activation.
Pyrogenicity	The device extract was non-pyrogenic under the conditions of the study.

3.6.2 Bench Testing Summary

Bench testing studies were conducted to verify the functional requirements identified for the device and to support mitigation for potential failure modes identified by design risk analysis.

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These studies supported the selection of test methods and specifications implemented during design and process transfer. These studies provided justifications for the "INSTRUCTIONS FOR USE" included in the proposed labeling, as well as the proposed ██ year device shelf life.

3.7   SUMMARY OF CLINICAL STUDIES

Following the introduction of NEW-FILL by Biotech Industries, S.A. to the European market as a wrinkle-filling product in 1999, independent investigators began to use the product for the treatment of facial contour defects associated with facial lipoatrophy. In September 2000, Dr. ████████ presented his preliminary data, which indicated that NEW-FILL was a safe and effective treatment for this condition. Other independent investigators also began using the product for the correction of the signs of facial fat loss in patients with lipoatrophy. These studies were conducted in Europe by HIV experts, and often used trained dermatologists or plastic surgeons to perform the injection procedures. The product also became available in the United States on a limited basis through Investigator-sponsored IDEs or through the non-profit buyers club Direct Access Alternative Information Resources (DAAIR).

The clinical studies included in this submission have been conducted by several independent investigators in both the European community and in the United States. In the United States, studies were conducted under Investigator-Sponsored Investigational Device Exemptions (IDEs).

Over 1500 patients have been treated with NEW-FILL (SCULPTRA) for the treatment of facial fat loss since the product was first available in 1999. Information has been obtained from the following sources:

Pivotal Data
- Detailed individual data from 79 patients who participated in two European studies (the VEGA study in ████ and the Chelsea & Westminster study in ████; [see Table 3-3]).

Supportive Data
- Interim reports of 282 patients who participated in US studies under investigator-sponsored IDEs or a compassionate use study (see Table 3-4).

Other Sources
- Information from 66 patients who were presented in poster presentations from studies conducted in France (see Table 3-5)
- Physician's accounts of over 1200 patients who received the product through the Direct Access Alternative Information Resources (DAAIR).

TABLE 3-3 PIVOTAL CLINICAL STUDIES

CLINICAL INVESTIGATION	PATIENT STATUS	BRIEF OVERVIEW
Short Title: **VEGA** Protocol: Study of impact of intradermal polylactic acid genal implants on HIV-positive patients with severe facial lipoatrophy Investigator: ▮▮▮▮ Institution: ▮▮▮▮ Start Date: June 2000 Stop Date: March 2003	54 patients consented (4 not treated) 50 patients (49 M / 1 F) treated 3 patients discontinued 47 patients completed 50 patients reported 41 patients authorized access to data	Two years of effectiveness and safety data are presented in a detailed clinical study report (see Appendix 12.2.1). These data include objective dermal ultrasound measurements of the treatment area and adverse event data.
Short Title: **Chelsea & Westminster Study** Protocol: A randomised open label study of Polylactic acid (NEW-FILL) injections for buccal fat pad wasting in persons with HIV related lipoatrophy Investigator: ▮▮▮▮ Institution: ▮▮▮▮ Start Date: June 2001 Stop Date: March 2002	30 patients (28 M / 2 F) consented and treated 30 patients completed the study, 29 patients reported 27 patients authorized access to data	Twenty-four weeks of effectiveness and safety data are presented in a detailed clinical study report (see Appendix 12.2.2). These data include objective dermal ultrasound measurements of the treatment area and adverse event data, as well as follow-up safety data for 1.5 to 2 years.

TABLE 3-4 SUPPORTIVE CLINICAL DATA

CLINICAL INVESTIGATION	REGULATORY STATUS	PATIENT STATUS	BRIEF OVERVIEW
Short Title: APEX001 Protocol: Compassionate Use of Facial Intradermal Implants of NEW-FILL® in Persons with HIV-Associated Lipoatrophy of the Face Investigator: ▓▓▓▓ Institution: ▓▓▓▓ Start Date: May 2001 Stop Date: ongoing	Investigator-sponsored study in US	100 male patients consented (4 not treated) 96 patients treated 24 patients discontinued 2 patients died 38 patients completed 32 patients ongoing	Safety and effectiveness data are presented for these patients in a detailed interim report (see Appendix 12.2.3). Data for all patients treated through August 2003 are included.
Short Title: APEX002 Protocol: Use of Intradermal Implants of NEW-FILL® in Persons with HIV-Associated Lipoatrophy of the Face Investigator: ▓▓▓▓ Institution: ▓▓▓▓ Start Date: 18 Feb 2002 Stop Date: ongoing	Investigator-sponsored study in US of device under IDE ▓▓▓▓	100 male patients consented (1 not treated) 99 patients treated 24 patients discontinued 34 patients completed 41 patients ongoing	Safety and effectiveness data are presented for these patients in a detailed interim report (see Appendix 12.2.4). Data for all patients treated through September 18, 2003 are included.

TABLE 3-4 SUPPORTIVE CLINICAL DATA (CONTINUED)

CLINICAL INVESTIGATION	REGULATORY STATUS	PATIENT STATUS	BRIEF OVERVIEW
Title: Mest Study	Investigator-sponsored study in US of device under IDE ▉	95 patients consented	Safety and effectiveness data are presented for these patients in a detailed interim report (see Appendix 12.2.5). Data for all patients treated through June 2003 are included.
Protocol: Safety, Efficacy and Impact of Intradermal NEW-FILL® Implants in Persons with HIV-Associated Lipodystrophy		87 patients treated (85 males/2 females)	
Investigators: ▉		7 patients awaiting treatment	
Institution: ▉	▉	1 patient discontinued	
Start Date: 23 July 2002		94 patients ongoing	
Stop Date: ongoing			

TABLE 3-5 OTHER SOURCES OF CLINICAL DATA

INVESTIGATOR	SOURCE/ STATUS	PATIENT STATUS	BRIEF OVERVIEW
Short Title: Amard Study **Protocol:** The effects of Polylactic Acid (PLA) (NEW-FILL®) as Therapy for Lipatrophy of the Face **Investigators:** ▉ **Institution:** ▉ **Start Date:** not reported **Stop Date:** not reported	Investigator-sponsored study in Europe of CE marked device ▉	33 males — data reported for 26 patients	Data from a poster presented at the 2nd International Workshop on Adverse Drug Reactions and Lipoatrophy in HIV held in Toronto, Canada 13, 14, 15 of September 2000. These data included objective dermal ultrasound measurements of the treatment area (see Appendix 12.2.6).
Short Title: Lafaurie Study **Protocol:** Treatment of facial lipoatrophy with NEW-FILL® in HIV-infected patients **Investigator:** ▉ **Institution:** ▉ **Start Date:** June 2001 **Stop Date:** ongoing	Investigator-sponsor study in Europe of CE marked device	40 patients (36 M / 4 F) Ongoing study — to enroll up to 123 patients	Safety and efficacy data from a poster presented at the 10th Conference on retroviruses and opportunistic infections; Boston, MA; February 2003. These data include objective measurements of the treatment area as measured by three-dimensional digital surface photo-grammetry (see Appendix 12.2.7).

3.7.1   Pivotal Studies

Two separate pivotal studies were independently conducted in Europe with commercially available NEW-FILL (SCULPTRA). Both the VEGA and Chelsea & Westminster studies were hospital-based clinical trials initiated and carried out by hospital site personnel. Neither study was sponsored by Dermik Laboratories, and the studies were clinically complete before Dermik acquired access to the data. Dermik contracted a contract research organization to retrospectively monitor and verify data from patients who authorized access to their medical records. For the VEGA study, 41 of the 50 patients authorized access to their data, and 27 of the 30 subjects in the Chelsea & Westminster study allowed Dermik representatives to retrospectively monitor and verify the source data. In addition, these patients also authorized the US FDA access to their source medical records for inspection.

Both the VEGA and the Chelsea & Westminster studies were open-label. The Chelsea & Westminster study was a randomized study, where patients were randomly assigned at Baseline to the Immediate Treatment Group, or to the Delayed Treatment Group (with NEW-FILL treatment delayed until Week 12 of the study). This design allowed the Delayed Treatment Group to act as a negative control to the Immediate Treatment Group, but still allowed all participating subjects to receive treatment for their facial lipoatrophy. Both studies received favorable approvals from their hospital ethics committees.

While these clinical studies were conducted outside of the US, the patient population with the condition of lipoatrophy is similar to that found in the US in terms of demographics and in terms of HIV antiretroviral treatments. Therefore, results of these studies would have application both in Europe and in the US.

Both studies had similar patient demographics. The criteria required of the target patient population in the two studies noted above included, but was not limited to, the following:

- clinically significant lipoatrophy of the face
- HIV-positive patients over 18 years of age
- non-pregnant or non-lactating females
- no active facial infections, herpes labialis, cutaneous Kaposi's sarcoma of the face
- no recent filler material or injections into the face

The complete study reports for the above-mentioned trials, with individual patient data listings and summary tables, are located in Appendix 12. These reports include data for all 50 patients entered into the VEGA study and 29 of the 30 patients entered into the Chelsea & Westminster study.

Similarities and/or differences of the two pivotal studies are noted in Table 3-6 below:

TABLE 3-6 STUDY COMPARISON OF THE VEGA AND CHELSEA & WESTMINSTER STUDY

	VEGA Study	Chelsea & Westminster Study
Patient Accountability	• 50 treated • 3 discontinued • 47 completed • 41 retrospectively source verified	• 30 treated • 30 completed • 29 reported (1 declined data disclosure) • 27 retrospectively source verified (2 declined data access)
Demographics	• 49 males/1 female • Mean age = 44.9 • Mean duration of HAART = 8.6 years • Mean baseline CD4 count = 397.1	• 28 males / 2 females • Mean age = 41 • Mean duration of HAART = 5.1 yrs • Mean baseline CD4 count = 473.6
Product use	• Reconstitution – 3 ml of sterile water • 3 to 6 treatment sessions • 1 vial per cheek for the majority of treatment sessions • Single physician injector (dermatologist)	• Reconstitution – 1 ml lidocaine, 2 ml sterile water • 3 treatment sessions for all patients • 1 vial per cheek per session • Single physician injector (plastic surgeon)
Study Procedures	• Laboratory parameters • Visual analog scale for well-being • Photographs • Facial Doppler Ultrasound	• Laboratory parameters • Anxiety/Depression scale (HAD) • Visual analog scale of severity of body shape change • Photographs • Facial Ultrasound
Time course	• Screening • Treatment sessions – Day 0, 15, 30, 45 and 60 (if needed) some patients had one additional treatment session • Follow-up visits – Weeks 12, 24, 48, 72 and 96	• Screening • Treatment sessions – Weeks 1, 2 and 4 (immediate group); Weeks 12, 14, and 16 (delayed group) • Follow-up visits – Weeks 12 and 24 • Additional post-study information obtained at ~1.5 years after the study
Endpoints	• Mean change in total cutaneous thickness (TCT) from baseline at weeks 8, 24, 48, 72 & 96 by ultrasound • Proportion of responders (TCT greater than 10 mm) at Week 24 • Median change in QOL from baseline at weeks 12, 24, 48, 72 and 96 • Tolerance	• Buccal skin thickness by ultrasound • Change in facial appearance lipoatrophy grade as assessed by physician and patient • Change in viral load and CD4 count • Change in blood chemistry parameters • Adverse events
Beneficial Changes	• Significant increases in the total cutaneous thickness from baseline • Improvements in quality of life (VAS of overall well-being) • Significant changes in facial appearance as noted in photographs	• Significant increases in buccal skin thickness from baseline • Change in facial appearance as assessed by VAS (visual analog scale) • Improvements in HAD (anxiety and depression scores)

Abbreviations: HAART: Highly Active AntiRetroviral Therapy

Both studies used objective ultrasound measurements and photographs as a means to establish the change in facial appearance. Statistical analyses were performed as a change from baseline in both studies.

Demographics from both studies show very similar patient populations as shown in Table 3-7.

TABLE 3-7 DEMOGRAPHICS FOR THE VEGA AND CHELSEA & WESTMINSTER STUDIES

	VEGA N=50	Chelsea & Westminster N=29
Sex	49 male / 1 female	27 male / 2 female
Age (mean, range)	44.9, 33 – 58	41, 32 - 60
Race	84% Caucasian 2% Black African 6% Hispanic 4% North African 4% Caribbean	72% Caucasian 3% Black 24% Hispanic
Duration of HAART Mean and range	8.6 years (1.1 – 14.1)	5.1 years (1.8 – 9.9)
Baseline CD4 count Mean and range	397.1 (127 – 807)	473.6 (188 – 908)

Abbreviations: HAART – Highly Active Anti-Retroviral Therapy

The number of treatment sessions for each study is noted in Table 3-8. Treatments were given in the cheek (also known as buccal or genal area) for both studies and usually one vial (3cc) was injected into each cheek. Injections were occasionally given in other facial areas (i.e., temples) in the VEGA study. Additionally, injections of less than 3 cc were given on some occasions.

TABLE 3-8 NUMBER OF INJECTION SESSIONS IN THE VEGA AND CHELSEA & WESTMINSTER STUDIES

TREATMENT SESSIONS	VEGA N=50	Chelsea & Westminster N=29
3	4 (8%)	29 (100%)
4	24 (48%)	-
5	19 (38%)	-
6	3 (6%)	-

Both studies captured adverse events throughout the study. Events captured included treatment-related and non-treatment-related adverse events. The treatment-related safety profile for both studies is similar, as noted in Table 3-9. Further safety and effectiveness information on these studies is provided in Sections 8.5 and 8.6, respectively, in this submission.

TABLE 3-9 INCIDENCE OF TREATMENT-RELATED ADVERSE EVENTS OBSERVED IN THE VEGA AND CHELSEA & WESTMINSTER STUDIES

ADVERSE EVENT	VEGA N = 50	CHELSEA & WESTMINSTER N = 29
Injection site nodule	26 (52%)	9 (31%)
Injection site bleeding/hematoma*	15 (30%)	1 (3%)
Injection site bruising	3 (6%)	11 (38%)
Injection site edema	2 (4%)	2 (7%)
Injection site discomfort	0	3 (10%)
Injection site inflammation	0	3 (10%)
Injection site erythema	0	3 (10%)
Injection site induration	0	1 (3%)
Injection site tenderness	0	1 (3%)
Injection site infection**	0	1 (3%)
Injection site lesion***	0	1 (3%)
Overall Incidence	35 (70%)	17 (59%)

*MedDRA preferred coding of Injection Site haemorrhage
**MedDRA preferred coding of Infection NOS (not otherwise specified)
***MedDRA preferred coding of Skin Lesion NOS (not otherwise specified)
Source: Individual study reports

There were no reported treatment-related serious adverse events (SAEs) in either study. There were six non-related SAEs in the VEGA study that are detailed in the study report located in Appendix 12.2.1.

There were no reported device failures, device extractions, or patient complaints for either study.

3.7.1.1 Pivotal Study Effectiveness Results – VEGA Study

Every patient treated with NEW-FILL (SCULPTRA) experienced increases in dermal thickness in the treatment area (minimum increase of 2.2 mm; refer to Table 3-10 below), and significant increases above baseline values of mean total cutaneous thickness (TCT) were noted at all time points (Weeks 8, 24, 48, 72 and 96) during the study. These data are also presented graphically in Figure 3-1 below. The mean increases above the baseline values ranged from 5.2 mm to 7.2 mm over the follow-up period (statistically significant, $p < 0.001$, at all time points). The mean TCT increased for up to and including Week 48 measurement time point, and the increases were sustained until the end of the study (Week 96) without any major complications.

TABLE 3-10 CHANGE FROM BASELINE IN TOTAL CUTANEOUS THICKNESS (MM) BY VISIT, PARAMETRIC ANALYSIS: ALL PATIENTS

Visit	n	Baseline Mean (SD)	Treatment Mean (SD)	Change From Baseline (mm)			
				Mean (SD)	(Min, Max)	p-value[a]	Responder* n (%)
Day 60 (Week 8)[b]	48	3.0 (0.6)	8.2 (1.7)	5.2 (1.7)	(2.2, 8.7)	<0.001	9 (18.8)
Week 24 (Month 6)	50	3.0 (0.6)	9.4 (1.5)	6.4 (1.6)	(3.0, 9.1)	<0.001	19 (38.0)
Week 48 (Month 12)	49	3.0 (0.6)	10.2 (1.2)	7.2 (1.3)	(4.3, 9.6)	<0.001	30 (61.2)
Week 72 (Month 18)	48	3.0 (0.6)	10.2 (1.2)	7.2 (1.3)	(3.5, 9.3)	<0.001	24 (50.0)
Week 96 (Month 24)	45	3.0 (0.6)	10.0 (1.3)	7.0 (1.4)	(3.9, 10.2)	<0.001	19 (42.2)

[a] The p-value is based on the paired t-test.
[b] Per Protocol Amendment 1, the Day 45 (Week 6) visit was changed to the Day 60 (Week 8) visit.
Note: ~~████████████████████████~~
Data Source: Table 2.2.2, 28OCT03 - V_FINAL, PARA_CHGTCT.SAS
            Table 2.1, 28OCT03 - V_FINAL, RESPOND.SAS
*Responder is defined as those patients who achieved total cutaneous thickness (TCT) of ≥10 mm

FIGURE 3-1 MEAN INCREASES ABOVE BASELINE IN TOTAL CUTANEOUS THICKNESS (mm) OBSERVED IN THE VEGA STUDY
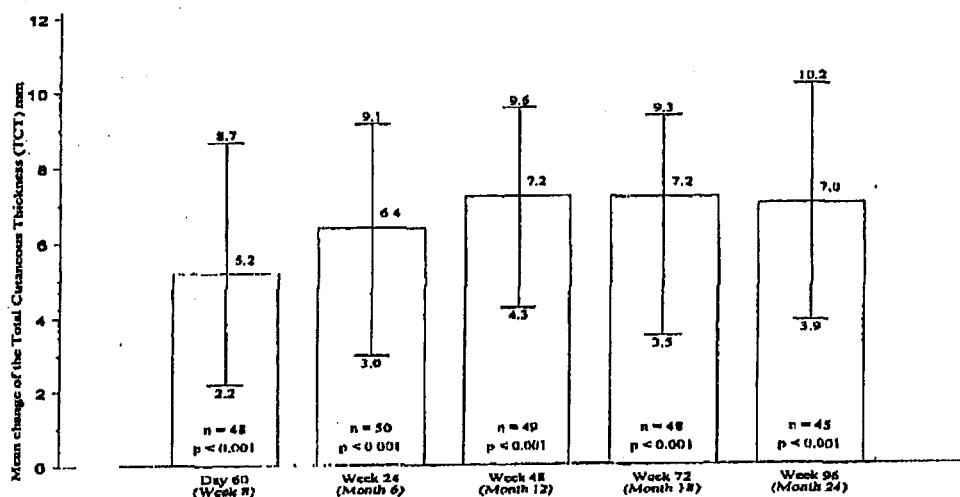
Extreme values: Max-Min: The p-value is based on the paired t-test.
Per Protocol Amendment 1, the Day 45 (Week 6) visit was changed to the Day 60 (Week 8) visit.

The objective and durable skin thickness improvements correlate with the clinical responses evident in the patient photographs, captured at treatment and follow-up visits (see Section 8.6.3.1.4). The contour deformities evident in prior treatment photos are greatly improved or eradicated in the follow-up photos further supporting the relevance of skin thickness as an outcome measure. Additionally, patient's sense of health and well being (measured by Visual Analog Scale) also improved. Statistically, significant increases in VAS were observed at Weeks 24 and 48.

Overall, the data obtained in the VEGA study demonstrate the correction of facial lipoatrophy with a statistically significant (p<0.001) increase in dermal thickness in the treatment area at all time points, coupled with visible improvements within the first few weeks to months of treatment and increases in Quality of Life at Weeks 24 and 48. This overall clinically significant improvement in the signs of facial lipoatrophy was sustained throughout the entire two-year follow-up period.

3.7.1.2 Pivotal Study Effectiveness Results – Chelsea & Westminster Study

Significant changes from Baseline in dermal thickness were recorded in the treated areas (left and right naso labia and cheeks) at Week 12 and 24 in the Immediate Treatment Group and at Week 24 only in the Delayed Treatment Group (see Table 3-11). These data are also presented graphically in Figure 3-2, Panels 1 and 2.

**TABLE 3-11 DERMAL THICKNESS CHANGES (MM) FROM BASELINE
CHELSEA & WESTMINSTER STUDY**

Dermal Thickness (mm)	Immediate Treatment Group N=14 Weeks 12 and 24			Delayed Treatment Group N=8 Week 12, N=13 Week 24			Between -Group p-value
	Baseline Mean	Change from Baseline Mean (SD)	Within-Group p-value	Baseline Mean	Change from Baseline Mean (SD)	Within-Group p-value	
Left Naso Labia							
Week 12	2.4	3.9 (2.1)	<0.001	2.4	0.1 (0.6)	0.774	<0.001
Week 24	2.5	5.3 (1.8)	<0.001	2.4	5.7 (2.1)	<0.001	0.525
Right Naso Labia							
Week 12	2.7	4.3 (2.9)	<0.001	2.3	0.2 (0.7)	0.448	0.001
Week 24	2.7	4.9 (2.3)	<0.001	2.5	6.0 (2.6)	<0.001	0.250
Left Cheek							
Week 12	2.4	4.1 (2.8)	<0.001	2.1	0.4 (0.4)	0.037	0.001
Week 24	2.5	4.9 (1.8)	<0.001	2.3	5.7 (1.8)	<0.001	0.247
Right Cheek							
Week 12	2.6	3.9 (2.4)	<0.001	2.3	0.3 (0.4)	0.121	<0.001
Week 24	2.6	4.9 (2.3)	<0.001	2.4	5.5 (2.3)	<0.001	0.487

Significant values (p <0.05) are bolded.
Source Data: Chelsea & Westminster Report; Table 2.1, 23OCT03 – V_FINAL, CHGULTRA/V_TABLE2_1/ V_TABLE2_1

Significant changes from Baseline (p<0.001) in dermal thickness were observed in the areas (left and right naso labia and cheeks) treated with NEW-FILL (SCULPTRA) at Week 12 and maintained through Week 24 in the Immediate Treatment Group. Significant changes from baseline were not observed until Week 24 (i.e., 12 weeks after initiation of treatment) in the

Delayed Treatment Group (p<0.001). Thus, the patients in the Delayed Treatment Group acted as a negative control to the Immediate Treatment Group at the Week 12 time point. A mean increase in dermal thickness of approximately 4-5 mm was observed twelve weeks after the initiation of treatment for both the Immediate Treatment Group (Week 12), and in the Delayed Treatment Group (Week 24). Areas that were not treated with the product (left and right mouth and zygoma) failed to show improvements in dermal thickness at any time point and therefore acted as an internal control.

As expected, differences in dermal thickness at treated sites were significantly different between groups at Week 12 (p<0.001). At Week 24 of the study, there were no differences in dermal thickness between the groups. This indicated that the treatment was equally effective in both groups, regardless of the arm to which they were randomized.

FIGURE 3-2 CHANGE IN DERMAL THICKNESS BY ULTRASOUND
CHELSEA & WESTMINSTER STUDY

PANEL 1 BASELINE TO WEEK 12

■ Immediate Treatment Group

● Delayed Treatment Group

NOTE: Error bars are 95% CI

PANEL 2 BASELINE TO WEEK 24

■ Immediate Treatment Group

● Delayed Treatment Group

NOTE: Error bars are 95% CI
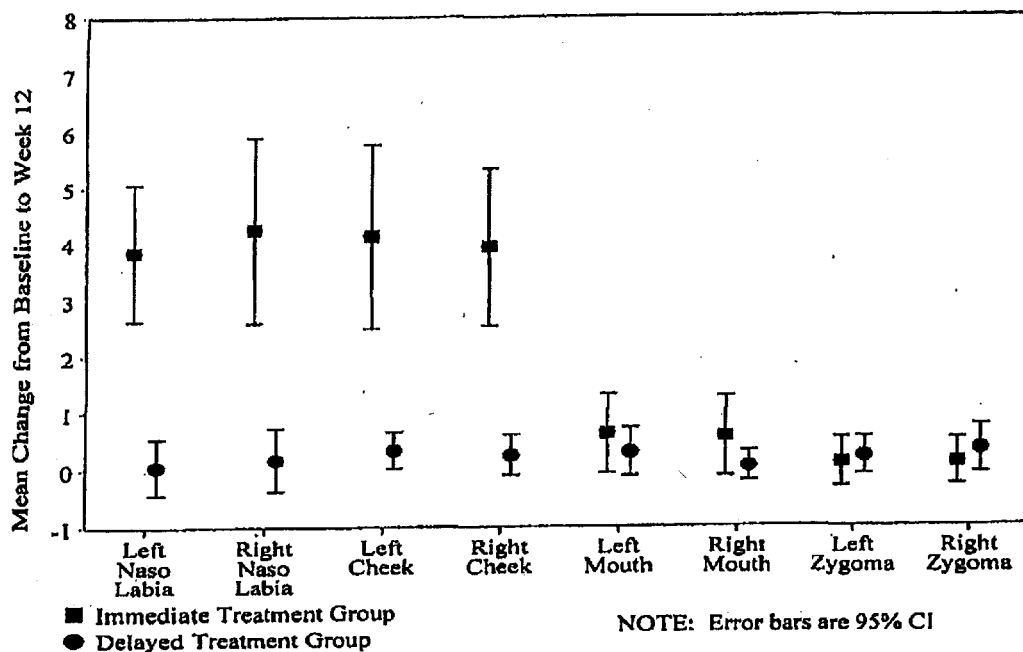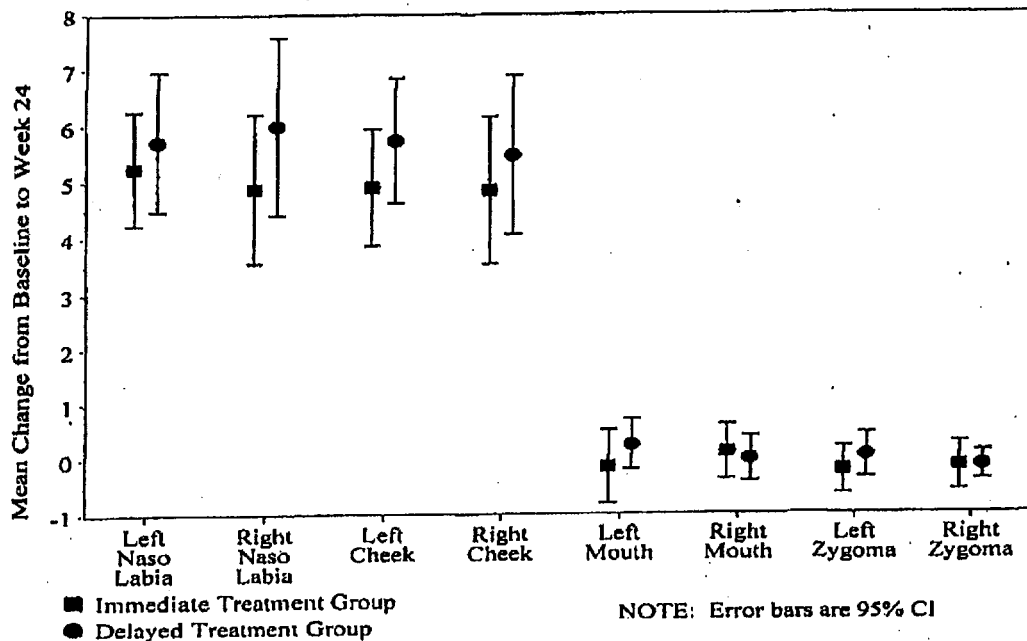
Source Data: Chelsea & Westminster report: Figure 1, 07NOV03, Figure_1.sas

Patient Self-Assessment

Similar to the dermal thickness observations above, significant (p<0.001) improvements in self-assessment visual analogue scores of the face were observed at Weeks 12 and 24 in the Immediate Treatment Group and at Week 24 in the Delayed Treatment Group.

Anxiety and Depression

Mean anxiety scores from the Hospital Anxiety and Depression (HAD) questionnaire were significantly improved in the Immediate Treatment Group at Weeks 12 and 24. At Baseline, mean HAD anxiety scores were within the range "suggestive of mood disorder" and the decreases in scores brought the patients' mean scores within the range of "normal". Mean HAD depression scores also showed improvements in the Immediate Treatment Group at Weeks 12 and 24 and at Week 24 in the Delayed Treatment Group (after treatment but not before).

3.7.2 Supportive Studies

Investigator-sponsored IDE studies are currently being conducted by ███████████████ (Study APEX002), and Drs. ████████████████, and these data are presented in this PMA as investigator reports. These investigators have given Dermik permission to reference their IDEs (refer to cross-reference letters attached to the PMA cover letter). ███████ also conducted a non-IDE compassionate use study (APEX001). These currently ongoing Investigator-sponsored IDE studies are similar in the patient populations studied and the inclusion /exclusion criteria. Both studies treat and evaluate HIV-positive patients with lipoatrophy of the cheeks and/or temples. Similarly both studies excluded those patients who had infection of the face, facial injections within the past three months, active Kaposi's Sarcoma of the face, signs or symptoms of lactic acidosis, pregnancy or breastfeeding, and treatment with interferon or systemic corticosteroids.

Data obtained from the ongoing Investigator-sponsored IDE studies in the United States offer supportive safety information on the device. No serious treatment-related adverse events were reported in the studies (although two patients died due to AIDS-related illnesses in the APEX001 study), and the adverse events observed in the studies are similar to those observed in the pivotal studies (VEGA and Chelsea & Westminster studies) (discussed in Section 3.7.1). No clinically significant laboratory abnormalities have been noted in either study to date. Adverse effects are generally mild, self-limiting and well tolerated by the patients.

Both studies queried the patients on "Injection Discomfort" via a rating scale. Patients rated their discomfort on a scale of 1 to 5. In the APEX 002 study (Dr. ███████), the mean discomfort rating reported by 99 subjects was 1.7 (1= minimal pain and 5= severe pain). Dr. ███ used a similar scale, with subjects reporting an average pain score of 1.7 for the treatment session (1= mild and 5= severe pain).

To date, there were no reported device failures or patient complaints in either study.

Preliminary results and conclusions shared by the investigators for these IDE studies are very similar. In their opinion, intradermal injections of NEW-FILL (SCULPTRA) provide a safe, well-tolerated and effective treatment for patients with HIV-associated lipoatrophy of the face.

Patients report a very high satisfaction with the treatment, which leads to an increase in confidence and an improved self-image.

Due to restrictions in the patient informed consent, these data were not monitored nor verified by Dermik Laboratories. However, the data collected for these Investigator Initiated IDE studies are available for FDA inspection in accordance with CFR Title 21 – Part 812.145 Inspections.

Interim Study Reports for these investigator-sponsored IDE studies can be found in Appendices 12.2.4 and 12.2.5.

Additional to the above sources of data, an interim report for a compassionate use study initiated by Dr. ████████ is also included in the PMA application (see Appendix 12.2.3). The objective of Dr. ████████ study was to gain access to the product and ascertain tolerability and safety of the product in the HIV population. These data add to the overall safety and effectiveness profile of NEW-FILL (SCULPTRA) as a long-lasting method for the correction of the signs of facial fat loss in patients with lipoatrophy.

Other sources of additional clinical information are also included in this submission. These include data from 66 patients who were presented in poster presentations from studies conducted in France, and physician's accounts of over 1200 patients who received the product in the US through the Direct Access Alternative Information Resources (DAAIR). This information is located in Section 8.3.4.

3.7.3 Overall Summary

In summary, several independently conducted studies of NEW-FILL (SCULPTRA) demonstrate that the product is considered a safe and effective treatment for the correction of the signs of facial fat loss in patients with lipoatrophy. Generally, patients presenting with severe facial lipoatrophy may require three to six injection sessions to achieve a desirable correction; however, the number of treatment sessions in a treatment course should be individualized for each patient. In addition, the amount of product injected at each session also needs to be individualized for each patient. Clinical experience with the product in Europe indicates that a gradual and methodical treatment approach should be used (i.e., treat, wait, and assess). Generally, two vials of reconstituted product (one vial for each side) will be needed for each treatment session of the depressed buccal (cheek) area in cases of severe facial fat loss.

The clinical utility of SCULPTRA as a treatment to correct the signs of facial fat loss in patients with lipoatrophy has been demonstrated with valid scientific evidence. Data supporting the clinical utility are derived primarily from two prospective clinical studies (VEGA and Chelsea & Westminster), each with extended follow-up periods (up to two years). In these studies, SCULPTRA demonstrated an acceptable safety profile in HIV seropositive patients. Treatment-related safety events were generally limited to transient events associated with the immediate injection procedure. Long-term adverse effects, even with a follow-up period of up to two years,

were limited to asymptomatic, small, but palpable nodules at the injection site. The effectiveness of SCULPTRA was also clearly demonstrated in these trials. For each study the clinical endpoints were based upon objective measurements of dermal thickness. The studies demonstrated highly significant increases in dermal thickness (up to 2 to 3 times baseline values). In the VEGA study, the increases in dermal thickness throughout the study were also associated with visible corrections of the volume defects as demonstrated by patient photographs (i.e., visible improvement in outward appearance). The clinical utility of SCULPTRA is also supported by improvements in Quality of Life (VEGA study) and measures of anxiety and depression (Chelsea & Westminster study). Therefore, valid scientific evidence presented in this PMA supports the safety, effectiveness, and clinical utility of SCULPTRA for the correction of signs of facial fat loss in patients with lipoatrophy.

3.8   CONCLUSIONS DRAWN FROM THE STUDIES

Clinical data from the pivotal studies indicate that:

- A treatment course of SCULPTRA is an effective and safe method of treating the signs of facial fat loss in HIV-positive patients with lipoatrophy.
- Facial injections with SCULPTRA significantly improve the signs of facial fat loss in patients with lipoatrophy as demonstrated by increases from baseline in dermal thickness within the first few treatment sessions. These clinically significant and visibly noticeable improvements in dermal thickness are sustained for up to two years following the first treatment session.
- Clinically significant increases in dermal thickness are accompanied by significant improvements in patient Quality of Life (i.e., overall well-being), self-assessments of the facial area, and measures of anxiety and depression.
- An individualized treatment course of multiple injection sessions of SCULPTRA offers a safe and effective treatment of the signs of facial loss in patients with lipoatrophy that may help alleviate the psychological and social consequences of facial lipoatrophy.
- Treatment-related adverse events are generally limited to transient events associated with the immediate injection procedure (e.g., injection site discomfort, bleeding, bruising, inflammation, and edema). Long-term adverse effects, even with a follow-up period of up to two years, were limited to asymptomatic, small but palpable nodules or indurations in the treatment area.

3.8.1   Risk/Benefit Analysis

SCULPTRA presents a favorable risk/benefit ratio for the treatment of the signs of facial fat loss in patients with lipoatrophy. Identified risks are typically transient, related to the immediate injection process or typically have minor consequence (small, non-visible, asymptomatic nodules). Careful adherence to product use instructions can mitigate most of these risks. Benefits of treatment with SCULPTRA are significant, as measured by either quantitative (increase in skin thickness) or qualitative (restoration of natural facial contours) outcomes. Results are reliable, with significant improvements noted in virtually all patients studied, and durable, lasting for approximately two years after the initial treatment session. Therefore, SCULPTRA may be considered as having an acceptable risk to benefit ratio for its intended use.

3.8.2 Discussion of Reasonable Assurance of Safety and Effectiveness for the Intended Use

It is Dermik's position that the data presented in this submission constitute valid scientific evidence of the safety and effectiveness of the product in the intended population.

The studies were conducted independently by hospital-based personnel and the patient benefits are substantiated by objective measures such as ultrasounds. In addition, photographs of the patients clearly document the benefits of the device. Highly significant dermal thickness changes from baseline were observed, and the majority of the patients significantly responded to the treatment. In addition to the detailed clinical study reports provided for the pivotal studies, poster presentations and publications from the use of the product by other European physicians supports the findings of the VEGA and the Chelsea & Westminster studies. Data provided in interim reports of Investigator-sponsored studies conducted in the United States also corroborate the clinical findings of the European studies.

4   DEVICE DESCRIPTION

4.1   DEVICE NAME AND INTENDED USE

The proposed name for the device is SCULPTRA (injectable poly-L-lactic acid).

The indication for use for SCULPTRA is proposed as follows:

> SCULPTRA™ is intended to correct shape and contour deficiencies resulting from facial fat loss (lipoatrophy) in people with human immunodeficiency virus.
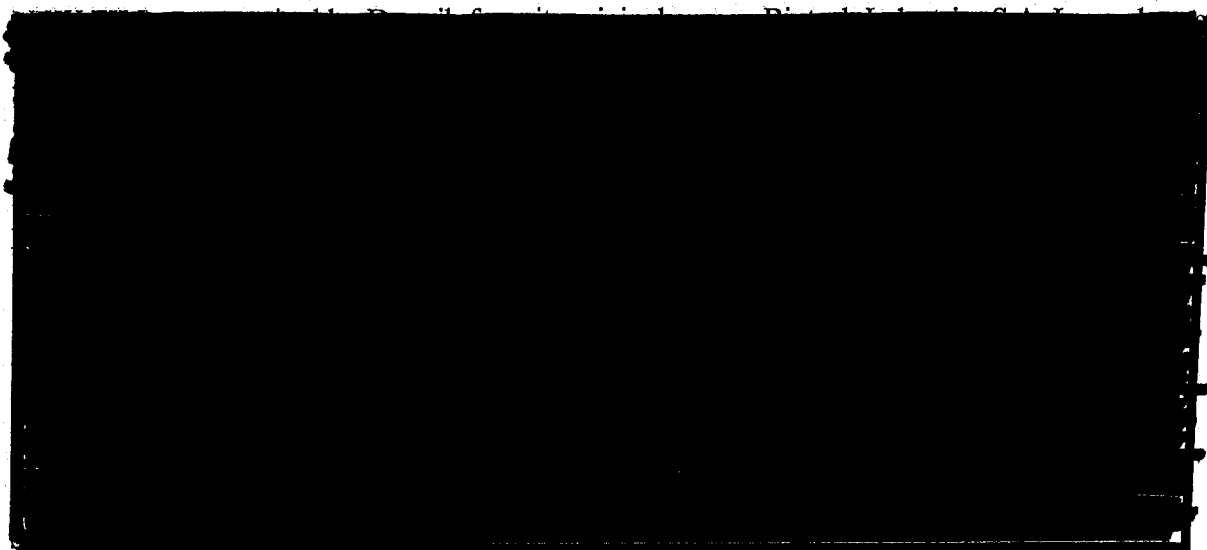
4.2   DEVICE COMPONENTS AND PURPOSE OF EACH COMPONENT

4.2.1   Description of Device

SCULPTRA, a sterile injectable medical device, is provided in a carton, which contains two ▮▮▮ ▮▮▮▮▮▮ glass vials of equal amounts of lyophilisate. The lyophilisate consists of non-pyrogenic mannitol, sodium carboxymethylcellulose, and microparticles of poly-L-lactic acid (PLLA). Before use, the lyophilisate is reconstituted with 3 mL of sterile water for injection, USP (SWFI), which is provided by the end-user. ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮.

TABLE 4-1 COMPONENTS OF SCULPTRA

Component	Amount per ▓▓▓▓ vial	Composition as ▓▓▓▓▓▓	Concentration after Reconstitution in 3 mL SWFI (%)
PLLA	▓▓▓	▓▓	▓▓
Sodium Carboxymethylcellulose, USP	▓▓▓	▓▓	▓▓
Non-pyrogenic mannitol, USP	▓▓▓	▓▓▓	▓▓▓
Sterile Water for Injection, USP	▓▓▓	▓▓▓	▓▓▓
Total	▓▓▓▓	▓▓▓	▓▓▓

Abbreviations: N/A = not applicable; PLLA = poly-L-lactic acid; SWFI = sterile water for injection

A picture of the device is shown in Figure 4-1.

FIGURE 4-1 PICTURE OF SCULPTRA
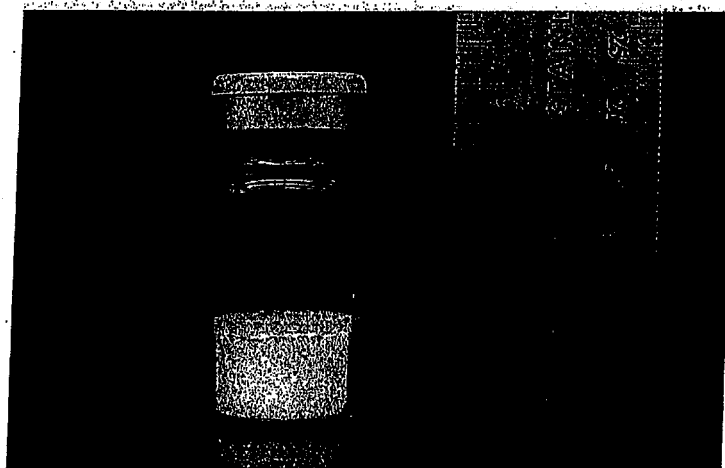
4.2.2 Poly-L-Lactic Acid

PLLA is supplied as ▓▓▓▓▓▓▓▓ provides the durable attributes of treatment with SCULPTRA. Polylactides have been widely used for many years in different types of medical devices such as intra-bone implants, resorbable sutures, and in soft tissue implants.[1,2,3] Polylactic acid polymers are also used in vectors for sustained-release injectable formulations, such as Lupron Depot® products, in which the drug substance is embedded in the polylactide microspheres.

The biodegradability (i.e., resorbability) of polymers of alpha-hydroxy acids, such as PLLA, is affected ▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓

[black redaction box]

4.2.3 Sodium Carboxymethylcellulose

Sodium carboxymethylcellulose (NaCMC) is included in SCULPTRA as a [redacted] The hygroscopic properties of NaCMC allow it to be easily dispersed in water at all temperatures, forming clear, colloidal solutions.[7]

NaCMC is generally recognized as safe (GRAS) for use in food (21 CFR 182.1745). It is widely used in parenteral products; such as Lupron Depot®, Bicillin® LA, and Sandostatin LHR®. NaCMC is included in the FDA Inactive Ingredients Guide for intradermal, intramuscular, soft tissue and subcutaneous injections (CDER, January 1996).

4.2.4 Non-pyrogenic Mannitol

Non-pyrogenic mannitol is included in SCULPTRA [redacted] jection.

Mannitol is listed as GRAS for use in food (21 CFR 180.25). This ingredient is widely used in parenteral products, such as Lupron Depot®, Nutropin®, Actimmune®, Espar® and Navane®. Mannitol is included in the FDA Inactive Ingredients Guide for intradermal, intramuscular, intravenous and subcutaneous injections (CDER, January 1996).

4.2.5 Other User - Provided Supplies

The following supplies are used with SCULPTRA, but are to be provided by the end-user:

- 3 mL of sterile water for injection (USP) for reconstituting each vial of SCULPTRA
- Single-use sterile syringe for addition of sterile water to SCULPTRA
- 18 G sterile needle for addition of sterile water to SCULPTRA
- Single-use sterile syringe for retrieving reconstituted SCULPTRA from vial
- 18 G sterile needle for removing reconstituted SCULPTRA from vial
- 26 G sterile needle for injecting SCULPTRA

The INSTRUCTIONS FOR USE section of the Package Insert (see Section 9 Labeling) provides detailed instructions for use of all supplies with SCULPTRA.

4.2.6 Vial and Packaging

SCULPTRA will be provided as a lyophilized product in a clear ████████████████ vial sealed by a ████████████ stopper, which is covered by an aluminum seal with a gray flip-off cap. Each carton of SCULPTRA will contain two vials.

4.3   PRINCIPLES OF USE

The SCULPTRA product is a resorbable soft tissue augmentation device provided as a lyophilisate for the correction of the signs of facial fat loss in patients with lipoatrophy. This product requires hydration and suspension prior to use, and is delivered via injection into the subcutaneous or deep intradermal space of the area requiring augmentation.

From studies of other PLLA products, it is known that following implantation, PLLA elicits a tissue response, which typically involves mononuclear cells, macrophages, proliferating fibroblasts with increased collagen production, and mature vascularized fibrous capsules.[4] During its biodegradation and resorption, PLLA is gradually hydrolyzed into lactate monomers, which are ultimately converted to CO_2 and water.

In the clinical setting, the volume of SCULPTRA injected at each treatment session is tailored by the practitioner to fill the target areas without overcorrecting the soft-tissue defect. Implantation of SCULPTRA provides an immediate physical filling effect, followed by a temporary (within days) reappearance of the contour defect, as the soluble components are resorbed. The correction will then improve over the course of a few weeks, as the tissue responds to the PLLA microparticles (discussed in Section 4.4.1). Thus, SCULPTRA provides a measurable increase in dermal thickness of the treatment area over time.

A treatment course with SCULPTRA may consist of one or more treatment sessions, each separated by two or more weeks until the desired clinical effect is achieved. Clinical experience with the product in Europe indicates that a gradual and methodical treatment approach should be used (i.e., treat, wait, and assess). Generally, patients presenting with severe facial lipoatrophy may require three to six injection sessions to achieve a desirable correction. However, the number of treatment sessions in a treatment course should be individualized for each patient. The amount of product injected at each session also needs to be individualized for each patient.

The tissue response to the implant provides the correction of soft tissue defects, and a gradual increase in the volume of the depressed area is observed over the first few weeks to months. The clinical effects of the device tend to last for at least two years following the initial treatment session.

4.4   THE PRINCIPLE OF OPERATION OF THE DEVICE

4.4.1   Tissue Response to PLLA

[REDACTED]

Patients with the facial signs of lipoatrophy were studied. These patients had a visible loss of subcutaneous fat in the buccal area. Patients were treated with multiple treatment sessions until the desired clinical effect was achieved. Clinical experience with the product indicates that the practitioner should use a gradual and methodical treatment approach in order to individualize the treatment for each patient (*i.e.*, treat, wait, and assess). Ultimately, the complete treatment course (i.e. number of visits, time between visits, and amount of product injected) will be the product of a collaborative relationship between the practitioner and the patient. The treatment course will be based upon sequential treatment sessions until the patient's desired response is achieved.

SCULPTRA provides an immediate physical filling effect upon injection, followed within days by a temporary reappearance of the contour deficiency as the soluble components are rapidly resorbed. The long-term filling effect occurs as a result of the gradual cellular reaction to the durable PLLA microparticles. Patient expectations should be managed by the treating physician by explaining that the product may take multiple treatment sessions over a period of several weeks to achieve the desired results.

4.4.2 Resorption of PLLA

Implanted products containing polylactides have a long history of being biocompatible and bioabsorbable. After implantation of the SCULPTRA device, the PLLA in the injection site gradually degrades. The slow resorption of PLLA after the implantation of SCULPTRA [REDACTED]

[REDACTED]

4.5   STANDARDS

4.5.1   Mandatory Performance Standards

No mandatory performance standards have been promulgated for this device.

4.5.2   Voluntary Standards

The following standards have been applied to the development, testing, and manufacturing of SCULPTRA.

4.5.2.1   General Standards

EN 1441 Risk Analysis.
ISO 10993 and EN 30-993-1 Biological Evaluation of Medical Devices
EN 552 Sterilization

4.5.2.2   Manufacturing standards

FDA 21 CFR Parts 210 & 211
FDA 21 CFR Part 820
United States Pharmacopeia
European Pharmacopeia
ICH guideline
EU-guide GMP (Annex 1, Annex 8, Annex 11, Annex 15, Annex 16)
Military Standard
UNI 9910
UNI EN ISO 14644-1
UNI EN ISO 14644-2
Certified Weights SIT

4.5.2.3

4.5.2.5

4.5.2.6

4.6   REFERENCES

The following references are cited to support the Device Description section of this PMA. There are no references specific to SCULPTRA or NEW-FILL available for this section. The reference marked with an asterisk is provided as indicated. Copies of all other references are available upon request.

1. Kronenthal, R.L. "Biodegradable polymers in medicine and surgery," *Polymer Science and Technology*, 1975, v8, p119-37.

2. Kulkarni R.K.; Pani, K.C.; *et al.* "Polylactic acid for surgical implants," *Archives of Surgery*, 1966, v93, n5, p839-43.

3. Nakamura, S.; Ninomiya, S.; *et al.* "Polylactide screws in acetabular osteotomy," *Acta Orthopaedica Scandinavica*, 1993, v64, n3, p301-02.

4. *Gogolewski, S.; Jovanic, M.; Perren, S., M, *et al.* "Tissue response and *in vivo* degradation of selected polyhydroxyacids: Polylactides (PLA), poly(3-hydroxybutyrate) (PHB) and poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHB/VA)," *Journal of Biomedical Materials Research*, 1993, v27, p1135-1148. (see Appendix 10.4.1).

5. Rowe, R. C.; Sheskey, P. J.; Weller, P. "Aliphatic Polyesters," in: *Handbook of Pharmaceutical Excipients*. 4th ed. Washington D.C. American Pharmaceutical Association; 200, p19-22.

6. ███

7. Rowe, R. C.; Sheskey, P. J.; Weller, P. "Carboxymethylcellulose Sodium," in: *Handbook of Pharmaceutical Excipients*. 4th ed. Washington D.C. American Pharmaceutical Association; 2003, p97-100.

8. Rowe, R. C.; Sheskey, P. J.; Weller, P. "Mannitol, " in: *Handbook of Pharmaceutical Excipients*. 4th ed. Washington D.C. American Pharmaceutical Association; 2003, p373-377.

9. Champe PC, Harvey RA, "Glycolysis," In: *Lippincott's Illustrated Reviews: Biochemistry*. 2nd ed. Philadelphia, Pa: J.B. Lippincott Company; 1994:p87-98.

10. Lodish, H.; Berk, A.; Zipursky, S.L.; *etal.* "Cellular energetics: glycolysis, aerobic oxidation, and photosynthesis," in: *Molecular Cell Biology*. 4th ed., New York, NY: W.H. Freeman and Company; 2000, Chapter 16, p622-626.

Dermik Laboratories
A Division of Aventis Pharmaceuticals Inc.

SCULPTRA™
(injectable poly-L-lactic acid)

BEFORE USING PRODUCT, READ THE FOLLOWING INFORMATION THOROUGHLY.

1. DEVICE DESCRIPTION

SCULPTRA™ is an injectable poly-L-lactic acid implant in the form of a sterile lyophilized cake. SCULPTRA contains microparticles of poly-L-lactic acid, a biocompatible, biodegradable, synthetic polymer from the alpha-hydroxy-acid family. SCULPTRA is reconstituted prior to use by the addition of Sterile Water for Injection, USP (SWFI) to form a sterile apyrogenic suspension.

2. INTENDED USE / INDICATIONS

SCULPTRA is intended to correct shape and contour deficiencies resulting from facial fat loss (lipoatrophy) in people with human immunodeficiency virus.

3. CONTRAINDICATIONS

SCULPTRA should not be used in any person who has hypersensitivity to any of the components of the product.

SCULPTRA should not be used in any person with active dermal inflammation or skin infection in or near the treatment area.

4. WARNINGS

- To avoid the risk of skin infarction or embolism of a blood vessel, do not inject into a blood vessel.

- Over-correction should be avoided, especially in the peri-orbital and the peri-oral areas.

- Do not inject into the red area of the lip.

5. PRECAUTIONS

- **SCULPTRA** should only be used by health care providers with expertise in the correction of volume defects after fully familiarizing themselves with the product and its complete package insert.

1

- **SCULPTRA** should only be used in the deep dermis or subcuticular layer. Avoid superficial injections.

- **SCULPTRA** vials are for single patient use only. Do not reuse or resterilize the vial. Do not use if package or vial is opened or damaged.

- Always reconstitute the lyophilisate with SWFI.

- For injection of **SCULPTRA**, use a 26 G sterile needle with single-use sterile syringes.

- The injection site should be cleaned with an antiseptic and should be free from inflammation or infection.

- As with all injections, patients treated with anti-coagulants may run the risk of a hematoma or localized bleeding at the injection site.

- The safety of **SCULPTRA** for use during pregnancy or in infants and children has not been studied.

- No studies of interactions of **SCULPTRA** with drugs or other substances or implants have been made.

- **SCULPTRA** should not be used in patients who form keloids.

6. ADVERSE EVENTS

Based upon data obtained through clinical studies, the known treatment-related risks for the use of **SCULPTRA** include immediate and transient injection-related events such as bleeding from the injection site, injection site tenderness or discomfort, injection site erythema or inflammation, bruising (hematoma), and injection site edema (swelling). Delayed events may include the formation of nodules or induration. In the pivotal clinical studies, the most commonly observed adverse event in the correction of facial fat loss (lipoatrophy) was the delayed occurrence of injection site nodules. Nodules were confined to the injection site and were typically non-visible, asymptomatic, small, but palpable. Nodules tended to occur within the first six months to one year after initial injection, and in some cases resolved spontaneously without specific treatment.

A summary of the treatment-related adverse events reported from two pivotal clinical studies is presented below.

INCIDENCE OF TREATMENT-RELATED ADVERSE EVENTS IN THE TWO PIVOTAL STUDIES

ADVERSE EVENT	STUDY 1 N = 50	STUDY 2 N = 29
Injection site nodule	26 (52%)	9 (31%)
Injection site bleeding/hematoma	15 (30%)	1 (3%)
Injection site bruising	3 (6%)	11 (38%)
Injection site edema	2 (4%)	2 (7%)
Injection site discomfort	0	3 (10%)
Injection site inflammation	0	3 (10%)
Injection site erythema	0	3 (10%)
Injection site induration	0	1 (3%)
Injection site tenderness	0	1 (3%)
Injection site infection	0	1 (3%)
Injection site lesion	0	1 (3%)
Overall Incidence	35 (70%)	17 (59%)

The following potential adverse events were reported at least once from additional sources of safety information and may also be associated with the use of SCULPTRA; however, these events were not observed in the pivotal clinical studies: nodules with inflammation or dyspigmentation, fever, malaise, injection site abscess, allergic reaction, dermatomyositis, injection site atrophy, face edema, Quincke's edema, injection site fat atrophy, photosensitive reaction, fatigue, injection site granuloma, and hypersensitivity reaction.

7. CLINICAL STUDIES

Summary of Clinical Studies

SCULPTRA has been found to be safe and effective in correcting the signs of facial fat loss in patients with lipoatrophy in two clinical studies.

A. Study 1

This open-label, non-comparative, single center study was conducted to determine the treatment effects of SCULPTRA on the signs of lipoatrophy of the face. Clinical effectiveness was determined by the measurement of total cutaneous thickness (TCT) measured over the course of the study by ultrasonography in the cheek area at Baseline, Weeks 8, 24, 48, 72 and 96.

Patients included in the trial were over 18 years of age, HIV-positive, with plasma HIV viral load less than 5,000 copies/mL for more than 3 months and were receiving concurrent antiretroviral therapy. All patients had subcutaneous adipose tissue of the cheek measuring less than or equal to 2.1 mm, as determined by ultrasound.

Demographics and Baseline Characteristics

Baseline characteristics of the fifty patients (49 males, 1 female) enrolled in this study include: signs of facial lipoatrophy (sunken cheeks) with a mean total cutaneous thickness of 3.0 ± 0.6 mm, and mean "Global Well-Being" scores of 6.6 ± 2.3 (arbitrary units ranging from 0 to 10). The majority of patients (84%) were Caucasian and between the ages of 33 and 58 years. All patients had little or no adipose tissue in the cheek area at baseline, indicating severe facial lipoatrophy (mean adipose thickness of 0.5 ± 0.7 mm, ranging from 0.0 to 2.1 mm).

Treatment

Injection sessions were approximately every two weeks, and the majority (86%) of the patients received four to five injection sessions. Generally, one vial of product reconstituted with 3 mL of SWFI was injected intradermally into multiple points of each cheek. The quantity of injected product depended upon the severity of the facial depression. Following injection, the skin was massaged to distribute the product evenly.

Results

Every patient treated with SCULPTRA experienced increases in dermal thickness in the treatment area (minimum increase of 2.2 mm noted at Week 8 visit, refer to the Figure below). Significant increases above baseline values of mean total cutaneous thickness (TCT) were noted at all time points (Weeks 8, 24, 48, 72 and 96) during the study. The mean increases above the baseline values ranged from 5.2 mm to 7.2 mm over the follow-up period (statistically significant, $p < 0.001$, at all time points). The treatment effect (increase in TCT) was evident as early as the 3rd to 4th treatment (measured at the Week 8 visit). The mean TCT increased significantly up to and including the Week 48 measurement time point, and these increases above baseline were sustained until the end of the study (Week 96).

MEAN INCREASES ABOVE BASELINE** IN TOTAL CUTANEOUS THICKNESS (MM)
OBSERVED IN STUDY 1

Extreme values: Max-Min; The p-value is based on the paired t-test.
* Approximate visit dates from first injection
** Baseline = 3.0 ± 0.6 mm
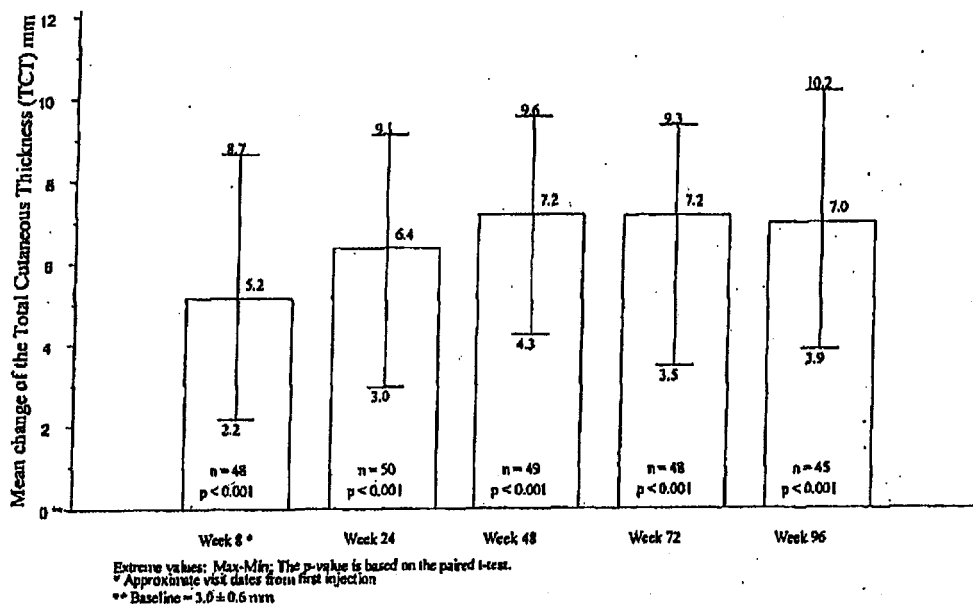
A Visual Analogue Scale (VAS) for evaluating Global Well-Being assessed the quality of life. Patients scored their physical and/or emotional status on a scale from 0 to 10 (10 being the highest score). Statistically significant improvements in Global Well-Being were observed at Weeks 24 and 48.

B. Study 2

This study was an open label, single center, randomized, 24-week study in 30 HIV- positive patients with facial lipoatrophy. Patients were randomized to either an Immediate or a Delayed Treatment Group (delayed by 12 weeks) with **SCULPTRA**. This design allowed the Delayed Treatment Group to act as a negative control to the Immediate Treatment Group, but still allowed all participating patients to receive treatment for their facial lipoatrophy. For the patients randomized to the Immediate Treatment Group, **SCULPTRA** injections were administered bilaterally in the buccal (cheek) areas on Day 1, and at Weeks 2 and 4. After facial ultrasounds were obtained, patients in the Delayed Treatment Group received injections at Week 12, 14 and 16 of the study. All patients completed the study at Week 24. Additional safety data were captured at a visit 1.5 to 2 years post-study.

The clinical endpoints were buccal skin thickness as assessed by ultrasound, patient rated change in appearance as assessed by Visual Analogue Scale (VAS) scores, and anxiety

and depression scores from the Hospital Anxiety and Depression (HAD) scale, at Baseline, Weeks 12 and 24.

Demographics and Patient Characteristics

Thirty patients (28 males, 2 females) were enrolled in the study. The majority of patients (72%) were Caucasian and between the ages of 32 and 60 years.

Treatment

For each treatment session each vial of **SCULPTRA** was reconstituted with 2 mLs of SWFI and 1 mL of 2% lidocaine to give a total volume of 3 mL. Up to 3 mL of the reconstituted product was injected into multiple points into the deep-dermis of the treatment area (buccal region) on each side of the face. Following injection, the skin was massaged to evenly distribute the product.

Results

Baseline dermal thickness in the treated areas ranged from 2.4 to 2.7 mm. Significant changes from Baseline (p<0.001) in dermal thickness were observed in the areas treated with **SCULPTRA** (left and right naso labia and cheeks) at Week 12 and maintained through Week 24 in the Immediate Treatment Group. Significant changes from baseline were observed at Week 24 (i.e., 12 weeks after initiation of the delayed treatment) in the Delayed Treatment Group (p<0.001). Thus, the patients in the Delayed Treatment Group acted as a negative control to the Immediate Treatment Group at the Week 12 time point. A mean increase in dermal thickness of approximately 4-5 mm was observed twelve weeks after the initiation of treatment for both the Immediate Treatment Group (Week 12), and in the Delayed Treatment group (Week 24). Areas that were not treated with the product (left and right mouth and zygoma) failed to show improvements in dermal thickness at any time point and therefore acted as an internal control. As expected, differences in dermal thickness at treated sites were significantly different between groups at Week 12 (p<0.001), since only the Immediate Treatment Group had received treatment at this time point. At Week 24 of the study, there were no differences observed in dermal thickness between the groups, indicating that the treatment was equally effective in both groups, regardless of the arm to which the patients were randomized.

Similar to the dermal thickness observations above, significant (p<0.001) improvements in self-assessment of facial appearance by visual analogue scores were demonstrated at Weeks 12 and 24 in the Immediate Treatment Group and at Week 24 in the Delayed Treatment Group.

Mean anxiety scores from the HAD questionnaire were significantly improved in the Immediate Treatment Group at Weeks 12 and 24. Mean HAD depression scores also showed improvements in the Immediate Treatment Group at Weeks 12 and 24 and at Week 24 in the Delayed Treatment Group (i.e., after treatment, but not before).

8. INDIVIDUALIZATION OF TREATMENT

The quantity of SCULPTRA used depends on the volume defect to be treated. A typical treatment for severe facial fat loss includes the injection of one vial of SCULPTRA per cheek per session. SCULPTRA provides a gradual but clinically significant increase in dermal thickness of the treated area. Full effects of the treatment regimen are evident within weeks to months. The patient should be reevaluated at an interval of not less than 2 weeks to assess the need for additional treatment sessions. Treatment effects may remain for up to 2 years after the first treatment session.

9. HOW SUPPLIED

SCULPTRA is supplied in a clear glass vial, which is sealed by a penetrable stopper, covered by an aluminum seal with a flip-off cap. Each carton of SCULPTRA contains two vials.

The contents of each vial should be reconstituted with 3 mL of SWFI. See INSTRUCTIONS FOR USE below.

COMPOSITION OF SCULPTRA

Each vial contains ▮▮▮▮ of SCULPTRA. The final composition of SCULPTRA consists of:

Component	Composition as Lyophilisate (%) (w/w)	Concentration after Reconstitution in 3mLs SWFI (%) (w/w)
Poly-L-Lactic Acid	▮▮▮	▮▮▮
Sodium Carboxymethylcellulose (USP)	▮▮▮	▮▮
Nonpyrogenic Mannitol (USP)	▮▮▮	▮▮▮
Sterile Water for Injection (USP)	N/A	▮▮▮

Abbreviations: N/A = not applicable

NDC 0066-1106-02

10. INSTRUCTIONS FOR USE

A. Reconstitution

The following supplies are used with SCULPTRA but are to be provided by the end-user:

- Sterile Water for Injection, USP
- 5 mL single-use sterile syringe for reconstitution
- 1-3 mL single-use sterile syringe for injections
- 18 G sterile needles (at least 2)
- 26 G sterile needles (several should be available)

SCULPTRA is reconstituted in the following way:

1. Remove the flip-off cap from the vial. If the vial, seal, or flip-off cap are damaged, do not use, and call Aventis Pharmaceuticals Inc. at 1-800-633-1610.

2. Attach an 18 G sterile needle to a sterile single-use 5 mL syringe.

3. Draw 3 mL of SWFI into the syringe.

4. Introduce the 18 G sterile needle into the stopper of the vial and slowly add the 3 mL of SWFI into the vial.

5. Let the vial stand for at least 2 hours (do not shake) to ensure that the lyophilisate is fully hydrated. SCULPTRA should be stored between 5°C and 30°C during and after hydration. Refrigeration is not required. The hydrated product is usable for 72 hours. Discard any material remaining after use or after 72 hours following reconstitution.

6. Immediately prior to injection of SCULPTRA, shake the vial until a uniform translucent suspension is obtained. SCULPTRA is now ready for use.

7. Clean the penetrable stopper of the vial with an antiseptic, and use a new 18 G sterile needle to withdraw an appropriate amount of the suspension into a single-use sterile syringe. Do not store the product in the syringe.

8. Replace the 18 G needle with a 26 G sterile needle before injecting the product into the deep dermis or subcuticular layer.

9. To withdraw remaining contents of the vial, repeat steps 6 through 8.

B. Patient Treatment

1. Before treatment with **SCULPTRA**, the patient should be informed completely of the indications, contraindications, warnings, precautions for use, possible side effects and mode of administration of **SCULPTRA**. A complete medical history should be taken to determine if the treatment is appropriate. Patients should be informed that more than one treatment session may be necessary to achieve the desired results.

2. As with all injectable products, universal precautions must be observed when there is a potential for contact with patient body fluids. The treatment session must be conducted with aseptic technique.

3. **SCULPTRA** should be injected using a 26 G sterile needle into the deep dermis or subcuticular layer of the area to be treated. The 26 G sterile needle, bevel up, is introduced into the skin at an angle of approximately 30-40 degrees, until the desired skin depth is reached. The angle is then lowered to advance the needle in the dermal plane. Prior to depositing **SCULPTRA** in the skin, a reflux maneuver is performed to assure that a blood vessel has not been entered. A thin trail of **SCULPTRA** is then deposited in the tissue plane as the needle is withdrawn. To avoid deposition in the superficial dermis, deposition is stopped before the needle bevel is visible in the skin. Multiple injections may be required to treat a targeted area. The depressed area should never be overcorrected in a treatment session.

4. Do not inject with needles smaller than 26 G. Avoid superficial injections, and do not bend the needle.

5. Shake the product in the syringe as needed to maintain a uniform suspension throughout the procedure.

6. The syringe should never be forced in order to inject the product. If the needle becomes blocked during injection, withdraw from the injection site and change the needle if necessary.

7. If the needle becomes clogged, draw a small amount of air into the syringe, shake to maintain a uniform suspension and expel a few drops of the product before resuming the injections.

8. If the 26 G needle becomes dull during a treatment session, replace the needle.

9. During the first treatment session with **SCULPTRA**, only a limited correction should be made. The patient should then be evaluated at no less than two weeks post-treatment to determine if additional correction is needed. The patient should be informed of the potential need for additional treatments at the first consultation.

10. After the injection session, an ice pack (avoiding any direct contact of the ice with the skin) should be applied to the treatment area in order to reduce swelling.

B. Patient Treatment (cont'd)

11. After the treatment, it is important to thoroughly massage the treated area(s) to evenly distribute the product.

12. The patient should periodically massage the treated area for several days after the treatment to promote a natural-looking correction.

13. Immediately following a treatment session with **SCULPTRA**, redness, swelling, and/or bruising may be noted in the treatment area. These signs typically subside in hours to a few days post treatment.

11. PATIENT INSTRUCTIONS

It is recommended that the following information be shared with patients:

- To report any adverse reactions, call Aventis Pharmaceuticals Inc. at 1-800-633-1610.

- Within the first 24 hours an ice pack (avoiding any direct contact of the ice with the skin) should be applied to the treatment area to reduce swelling. **SCULPTRA** may cause redness, swelling or bruising when it is first injected into the skin. This typically gets better in hours to a few days; worsening or prolonged symptoms or signs should be reported to the health care provider. The original skin depression may initially reappear, but the depression should gradually improve within several weeks as the treatment effect of **SCULPTRA** occurs. The treating health care provider will assess the need for additional **SCULPTRA** treatment sessions.

- Massage the treatment area daily, for several days following any treatment session, as instructed by the healthcare provider

- As with all injections, patients treated with blood thinners or aspirin-type products may run the risk of bruising or swelling in the treatment area.

- The safety of **SCULPTRA** for use during pregnancy or in infants and children has not been studied.

- No studies of interactions of **SCULPTRA** with drugs or other substances or implants have been made.

- Treatment with **SCULPTRA** can result in lumps or bumps in the treated area of the skin. These very small lumps may not be visible to the patient, but may only be noticed when pressing on the treated skin. Visible bumps, sometimes with redness or color change to the skin, have also been reported. Patients should report any side effects to their health care provider.

11. PATIENT INSTRUCTIONS (cont'd)

- Make-up may be applied a few hours post-treatment if no complications are present (e.g. open wounds, bleeding, and infection).

12. STORAGE

SCULPTRA should be stored at room temperature away from heat (maximum 30°C).

Refrigeration is not required.

13. STERILITY

SCULPTRA is packaged for single-use only. Do not resterilize.

IF THE VIAL, SEAL, OR THE FLIP-OFF CAP ARE DAMAGED, DO NOT USE AND CONTACT AVENTIS PHARMACEUTICALS INC. AT 1-800-633-1610.

14. CAUTION

Caution: Federal Law (USA) restricts this device to sale by or on the order of a physician or licensed healthcare practitioner.

ANY SIDE EFFECTS OR PRODUCT COMPLAINTS SHOULD BE REPORTED TO:
Aventis Pharmaceuticals Inc.
Bridgewater, NJ USA
1-800-633-1610

Patent pending
Prescribing Information as of November 2003(d).
Manufactured for:
Dermik Laboratories
A Division of Aventis Pharmaceuticals Inc.
1050 Westlakes Drive
Berwyn, PA 19312
USA
(1-800-633-1610)

Produced by:
Gruppo Lepetit S.p.A. 20020 Lainate, Italy

© 2003 Dermik Laboratories

9.2   VIAL LABEL

NDC 8044-1106-02

Sculptra™

Injectable
poly-L-lactic acid

Conc 367.5mg
Vial

DERMIK®
4 Ampuls

Store at room temperature.
Contents: If vial, seal or flip-off cap
are damaged, do not use. Pack-
ages for single use only, do not
resterilize. Read Physician Package
Insert prior to use. Caution: Federal
Law (USA) restricts this device to sale
by or on the order of a physician or
licensed healthcare practitioner.
Mfd for: Dermik Laboratories
Berwyn, PA 19312   ©2001
(1-800-633-1610)
Made in Italy   82010297

9.3   CARTON

NDC 0066-1106-01

Sculptra™
injectable poly-L-lactic acid

Two 367.5mg Vials

DERMIK®
✶Aventis

NDC 0066-1106-02

Sculptra™
injectable poly-L-lactic acid

Two 367.5mg Vials

DERMIK®
✶Aventis

NDC 0066-1106-02

Sculptra™
injectable poly-L-lactic acid

Two 367.5mg Vials

DERMIK®
✶Aventis

Sculptra™
injectable poly-L-lactic acid

FOR SUBCUTANEOUS OR DEEP INTRADERMAL INJECTION
Contains each Sculptra™ vial contains 367.5mg of a sterile lyophilized cake
which is reconstituted by the addition of Sterile Water for Injection (USP) to form
a sterile anisotropic suspension. The composition of Sculptra™ contains 94.48%
poly-L-lactic acid, 24.5% anhydrous sodium carboxymethylcellulose (USP) and 2.47% non-
pyrogenic mannitol (USP). Store at 15-30°C, room temperature away from heat.

Dosage and Administration: See Premium Package Insert.

• If defective, flip seal Cap or Cap not damaged, do not use
• Protected and Use once only
• For external use
• Read Premium Package Insert prior to use
Caution: Federal Law (USA) restricts this device to sale, by or on the order of a
physician or licensed healthcare practitioner

Patent pending
Mfd for: Dermik Laboratories
A Division of Aventis Pharmaceuticals Inc.
Berwyn, PA 19312 C2003
(1-866-633-1030)
Mfd by: Gattefossé Laperriot S.p.A.
20020 Lainate, Italy
Made in Italy

4800390003

Lot

Exp.

6 NONCLINICAL SECTION

6.1 DEVICE DEVELOPMENT HISTORY

NEW-FILL was approved by the French Notified Body G-Med (Groupement pour L' Evaluation des Dispositifs Medicaux – Department of Evaluation of Medical Devices) on November 25, 1999 as a Class III device under the category "Wrinkles Filling Product." This approval is based upon compliance with the requirements described in the European Directive 93/42/EEC. The approved CE Mark indication states:

> "NEW-FILL is suitable for increasing the volume of depressed areas, particularly to correct skin depression, such as in skin creases, wrinkles, folds, scars and eye rings. It is particularly useful for degenerative skin lesions due to skin aging."

Based on the European Community regulatory system for medical devices, marketing approval granted in one nation is valid for all participating EU nations. Additional registrations for NEW-FILL outside of the EU have also been granted. (see Section 3.4 Marketing History.)

Following the availability on the European market for the initial indication as a "Wrinkles Filling Product", several clinical studies were initiated to determine if NEW-FILL was acceptable for use in the correction of the signs of facial fat loss in patients with lipoatrophy. The pivotal studies, as discussed in the clinical section of this PMA, are the VEGA study conducted in ███████, initiated in June 2000, and the Chelsea-Westminster study conducted in ███████, initiated in June 2001.

NEW-FILL was acquired by Dermik from its original owner, ████████████████████████ ████████████████████ The manufacturing process was transferred from ███████ ███████████████████████████████████commercialization of the device in the US market. During its various stages of development, this product has been identified by several names. Early nonclinical studies, conducted by the original owner ███████ Laboratories, may refer to the product as ███████" or "NEW-FILL". Upon purchase of the product, the Dermik Laboratories development number ███████ as assigned, hence nonclinical studies conducted after the acquisition may refer to the product as "NEW-FILL" or ███████

The name "SCULPTRA", with the generic name "injectable poly-L-lactic acid", was selected as the brand or trade name for the product to be produced at the ███████ facility for the US market. Thus, depending on the timing of the study or the intent of the discussion, this PMA may refer to the device as ███████ NEW-FILL, ███████ injectable poly-L-lactic acid, or SCULPTRA. Pending FDA approval, ███████ ill be registered for the US market for the correction of the signs of facial fat loss in patients with lipoatrophy under the trade name SCULPTRA, generic name injectable poly-L-lactic acid.

Since its acquisition, Dermik has verified that SCULPTRA was developed in conformance with the Design Control provisions of the QSR (21 CFR 820.30). Dermik will ensure that the manufacturing of SCULPTRA is in compliance with the Medical Device Quality System Regulation.

Nonclinical safety assessment studies completed for NEW-FILL to obtain its approval in Europe were conducted in compliance with the ISO 10993 Standard, Biological Evaluation of Medical Device.

6.2

TABLE 6-1 DESIGN REQUIREMENTS

Design Input	Design Output Means/Test method	Acceptance Criteria

TABLE 6-1 DESIGN REQUIREMENTS (continued)

Design Input	Design Output Means / Test method	Acceptance Criteria
▮▮▮▮▮	▮▮▮▮▮	▮▮▮▮▮
	▮▮▮▮▮	▮▮▮▮▮
▮▮▮▮▮		▮▮▮▮▮
	▮▮▮▮▮	
	▮▮▮▮▮	▮▮▮▮▮
	▮▮▮▮▮	▮▮▮▮▮
	▮▮▮▮▮	▮▮▮▮▮
▮▮▮▮▮	▮▮▮▮▮	▮▮▮▮▮
▮▮▮▮▮	▮▮▮▮▮	▮▮▮▮▮
▮▮▮▮▮	▮▮▮▮▮	▮▮▮▮▮

*LMID = Local Material Identification

6.3 TECHNICAL RISK ANALYSIS

6.3.1 Analysis of Potential Failure Modes

As the basis of device evaluation studies and part of the overall process for managing medical device risk, Dermik performed a risk analysis using procedures which are in compliance with ISO/DIS 14971 Medical Devices – Risk Management – Part 1: Application of Risk Analysis to Medical Devices and EN 1441 Medical Devices - Risk Analysis. Dermik's Failure Mode Effects Analysis (FMEA) procedure was used to identify and assess the levels of risks in both the design and the manufacturing process of SCULPTRA. Dermik has completed the following risk analysis steps:

- identification of potential hazards associated with this device
- identification of causes (of hazards) and potential sources of causes
- assessment of the level of user risk for each hazard
- identification of mitigations in areas with unacceptable levels of user risk
- assessment of risk after mitigation efforts
- identification of key documents to record mitigation efforts

6.3.2 ███████████

Dermik's FMEA for risk analysis follows ███████████ which is provided in Appendix 11.4.3. Specific procedures applied to ██████ are summarized as follows:

███████████████████████████████████

6.3.2.1 Design FMEA

███████████████████████████████████

TABLE 6-2 RESULTS OF DESIGN FMEA

Part Name/ Function Description	Potential Failure Mode	Potential Effect(s) of Failure	Mitigation Action taken
████████	████████	████████e	████████
	████████	████████	████████
	████████	████████	████████
	████████	████████	████████
	████████	████████	████████

TABLE 6-2 RESULTS OF DESIGN FMEA (continued)

Part Name/ Function Description	Potential Failure Mode	Potential Effect(s) of Failure	Mitigation Action taken
▮	▮	▮	▮
	▮	▮	▮
▮	▮	▮	▮
	▮	▮	▮

TABLE 6-2 RESULTS OF DESIGN FMEA (continued)

6.3.2.2 █████████

███
███
███████████████████████████████████████

Table 6-3 Potential Process Failure Modes and Their Mitigation

Part Name/ Process Description	Potential Failure Mode	Potential Effect(s) of Failure	Mitigation Action Taken
██████	███████	████████	████████
█████	██████	███████	████████
███████	██████	██████ c	██████

6.3.2.3 Risk Analysis Conclusion

Dermik has concluded from the above risk analysis that user risk associated with SCULPTRA has been adequately mitigated to introduce the device to the U.S. market.

6.4 ████████████████

███
███
███████████████████████████████████

███
███

TABLE 6-4 DESIGN VERIFICATION STUDIES

Study name	Study Description	Conclusions
███████	████████████████	███████████████
███████	████████████████	███████████████
███████	████████████████	███████████████
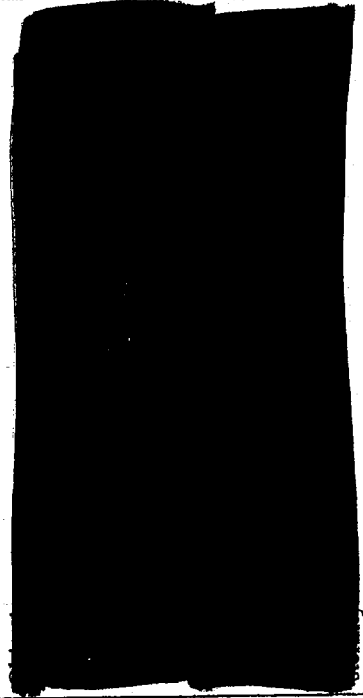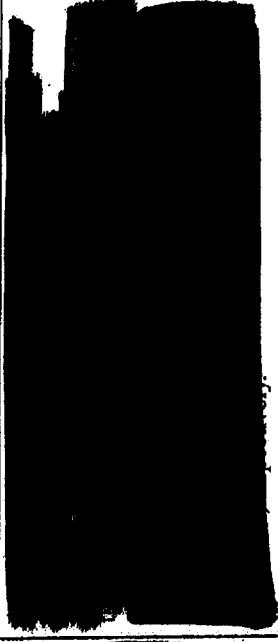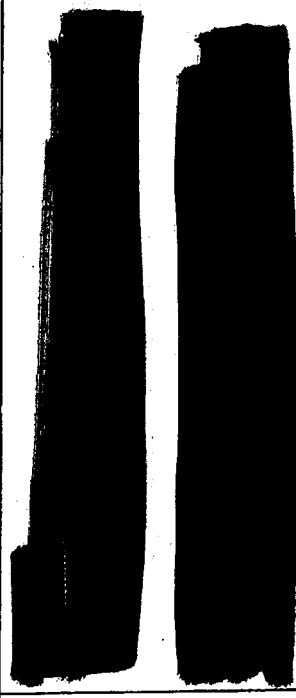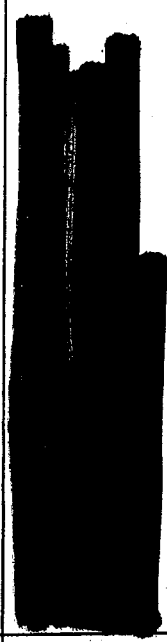
TABLE 6-4 DESIGN VERIFICATION STUDIES (continued)

Study name	Study Description	Conclusions
■■■■	■■■■■■■■	■■■■■■■■
	■■■■■■■■	■■■■■■■■
■■■■	■■■■■■■■	■■■■■■■■
		■■■■■■■■

TABLE 6-4 DESIGN VERIFICATION STUDIES (continued)

Study name	Study Description	Conclusions
██ ██	██ ██ ████████████	████████████
██	██ █████████	████████

TABLE 6-4 DESIGN VERIFICATION STUDIES (continued)

Study name	Study Description	Conclusions
███	███	███
███	███	███

6.4.1   Characterization of PLLA

The purpose of this characterization study, ███████████████████████████
███████ was to evaluate the chemical and physical characteristics of PLLA used for the
manufacture of NEW-FILL, and to evaluate and select the most relevant analytical methodologies
for the characterization of PLLA from various stages of processing.

The evaluation was performed and reported ████████████████████████ The report
summarizes the chemical and physical characteristics of █████████████████
PLLA used for the manufacture of NEW-FILL.

██
██
██
██
██

██
██
██

The results of this study support the definition of the test methods and specifications for design
transfer of PLLA. ███████████████████████████████████
██

Table 6-5 CHEMICAL AND PHYSICAL CHARACTERISTICS OF PLLA USED IN THE MANUFACTURE OF NEW-FILL

PLLA Characteristics	Analytical Technique	Stage of the Process	Impact of Process on PLLA Characteristics
████████	████████████	███████	█████████████
		██████████	████
█████████	████	██████	█████████████
		█████████████	█████████████
█████████	████	██████	█████████████
		█████████████	████████████
███████████	████	██████	████████████
		█████████████	████████████
█████████	█████████████	██████	█████████████
		█████████████	████████████

████████████████████████

6.4.2   Evaluation of PLLA and NEW-FILL® from Marketed Lots

The purposes of this characterization study ████████████████████████
██████████ere (1) to verify whether the retained samples of NEW-FILL, including those lots used in the clinical studies, met the currently approved shelf life of ██ months, and (2) to assess, retrospectively, the performance of the manufacturing process as part of the process FMEA.

██

██

[REDACTED]
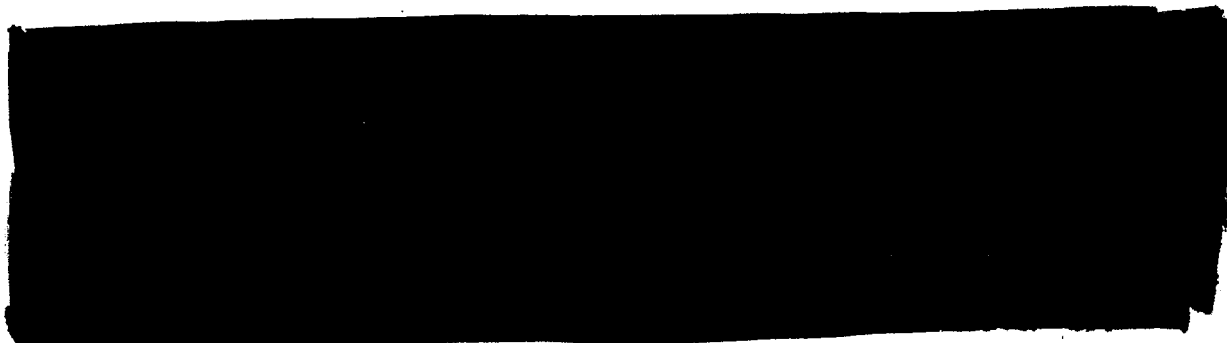
**Table 6-6 TESTS PERFORMED ON THE RETAINED SAMPLES
OF NEW-FILL MARKETED LOTS**

Test	Verification Purpose	Conclusion
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

6.4.3 In Vitro Degradation of PLLA

The purpose of the characterization study, [REDACTED] was to study the *in vitro* degradation of PLLA in simulated aqueous medium in order to project the half-life of PLLA *in vivo*. These experiments also provide supportive information for the product shelf life as outlined in the Product Functional Requirements.

It has been reported in the literature that polylactide microparticles degrade slowly over a period of months, even if incubated under simplified conditions in saline at 37°C (see Section 4.3.2). Since the initial degradation of PLLA *in vivo* is independent of any enzymatic system, an *in vitro* degradation study was conducted to project the half-life of PLLA *in vivo*. [REDACTED]
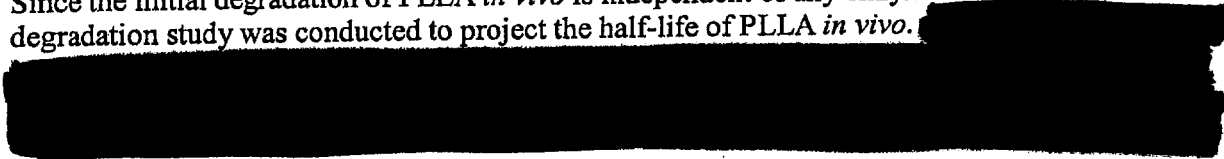
[REDACTED]

[REDACTED]

The results from the incubation in a phosphate buffer, simulating biological conditions, are consistent with the biodegradability of PLLA through non-enzymatic hydrolysis of the ester bonds described in the literature. [REDACTED]

6.4.4 Wetting and Syringeability [REDACTED]

The purposes of the characterization study, [REDACTED] were to (1) determine the wetting time required for reconstitution to obtain a uniform suspension in support of the "INSTRUCTIONS FOR USE" in the proposed product labeling, and (2) evaluate and verify the needle gauge suitable for the administration of the reconstituted product.

Wetting time requirement and syringeability [REDACTED] to support the "INSTRUCTIONS FOR USE" for the proposed SCULPTRA labeling. There are no noticeable differences in wetting time and syringeability among products reconstituted with [REDACTED] of sterile water for injection.

The 26G needle is the most practical option for injection. It can be used to easily deliver [REDACTED]

[REDACTED]

Based on these results, the "INSTRUCTIONS FOR USE" in the proposed labeling states that the product requires a minimum wetting time of [REDACTED] and the use of a 26G needle for administration. These instructions meet the design requirements for the product.

6.4.5 Syringeability of ████████ Using Force Gauge

The purpose of the characterization study, ██████████████████████████████ ███████████ was to demonstrate that ███████ is easily extruded through a 26G needle.

The most commonly used volume of injection of the reconstitute ███████ in the clinical setting ██

███

Clogging may occur during the extrusion of the reconstituted ████████ However, it can be easily alleviated by pulling air into the syringe, and inverting the syringe 4-5 times. The remaining suspension in the syringe could then be easily extruded.

The results of this study show that the product reconstituted after a ██ hour wetting time can be easily extruded through the 26G needle using the ████████████████ The outcome of this study confirms the recommendation for the ██ hour wetting time and the use of 26G needle for the injection of the product.

6.4.6 Stability of Reconstituted DL6049

The purpose of the characterization study, ████████████████████████████████ ██████████████ was to provide instructions for the storage and "in-use" period of ████████ following the reconstitution with ████████ This information will be included in the labeling as required by the Design Requirements.

Reconstituted samples were tested for ████████████████████████████████ at ██, ██, and ██ ████ after reconstitution. Reconstituted stability samples yielded consistently similar pH, inherent viscosity, and syringeability throughout the experiment. The product's container-closure system was shown to be able to maintain sterility for up to ████████ after reconstitution (after one puncture).

The product was shown to be physically, chemically and microbiologically stable for up to ████ ████ after reconstitution when stored between ████████████ which meets the design requirement for the establishment of the time period (at least ████████) and storage condition after reconstitution.

6.4.7   Validation of The Average Mass Specification

A design validation on the mass uniformity specification was conducted on NEW-FILL lots that were used in the ███.
These data were used to establish the commercial design specification for mass uniformity, which was determined to be ████████████████/ vial with a target██████████. All of the vials from lots used in the clinical studies met the mass uniformity specification. (see report DER03-114 [Appendix 10.2.7]).

6.4.8   Stability Study of NEW-FILL████████

████████month stability data were obtained from NEW-FILL lot███████, manufactured by███████ ████████ in ████████████. This stability study was conducted under the storage conditions outlined in the ████████████████. While this guidance is not specifically designed for medical devices, it is relevant to SCULPTRA. SCULPTRA is a sterile implant, which contains lyophilized poly-L-lactic acid (PLLA),███████████████████████████████in a vial, and is similar to many injectable drug products. This guidance is applicable because the

███
███
███ The container closure system must protect the lyophilisate from the moisture, ██████████████████████████████
████████████████████████

After██months of storage a███████████████████████████all samples met the proposed product specifications for product description, sterility, as well as pH and appearance of the reconstituted suspension. ██
███
███
███
███

6.4.9   Equivalence of SCULPTRA and NEW-FILL

The manufacturing process at██████████████████████████████████
████████was engineered to follow the same process steps as the process at██████████████ In both manufacturing sites, the following steps are utilized: 1)██████████████████████████
███
███
███
███
███

TABLE 6-7 COMPARISON OF BATCH SIZE

Manufacturing site				▇▇▇▇	▇▇▇▇
Component description	Supplier	Unit Formula	Batch quantity ▇▇▇▇	Batch quantity ▇▇▇▇	
Poly-L-Lactic Acid	▇▇	▇▇	▇▇▇	▇▇▇	
Sodium Carboxymethylcellulose, USP	▇▇	▇▇	▇▇▇	▇▇▇	
Pyrogen-free Mannitol, USP	▇▇▇▇	▇▇▇	▇▇▇	▇▇▇	
Sterile Water For Injection, USP	▇▇▇	▇▇▇	▇▇▇	▇▇▇	

TABLE 6-8 COMPARISON OF MANUFACTURING PROCESS

Description	NEW-FILL	SCULPTRA
▇▇▇	▇▇▇▇▇▇	▇▇▇▇▇▇
▇▇▇▇	▇▇▇▇▇▇	▇▇▇▇▇
▇▇▇▇	▇▇▇▇▇▇	▇▇▇▇▇
▇▇▇▇	▇▇▇▇▇	▇▇▇▇▇
▇▇▇	▇▇▇▇	▇▇▇▇
▇▇▇	▇▇▇	▇▇▇▇
▇▇▇	▇▇▇	▇▇▇
▇▇▇	▇▇▇	▇▇▇

The device design of SCULPTRA is equivalent to NEW-FILL ▇▇▇▇▇▇▇▇ ▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇ Each of the raw materials and components are the same grade and are sourced from the same suppliers. The primary package consists of the same ▇▇▇▇ with the identical ▇▇▇▇▇▇▇ from the same supplier. Even though the vial ▇▇▇▇▇▇▇▇▇ ▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇

6.4.9.1 Batch Size

▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇

6.4.9.2   Vial Size

[text redacted]

s
pr

6.4.9.7 Secondary Packaging

[text redacted]

6.4.9.8 Conclusion

[text redacted]

6.5 USEFUL LIFE

6.5.1

6.5.2 Proposed Stability Program

6.5.2.2

6.6   BIOLOGICAL TESTING

6.6.1

TABLE 6-9 COMPOSITION OF BATCHES USED IN THE
NON CLINICAL TOXICITY STUDIES

FORMULATION	LOT NO	FINISHED PRODUCT COMPOSITION				BIOCOMPATIBILITY STUDIES CONDUCTED
		▮▮▮▮▮				
▮	▮▮▮	▮▮	▮	▮▮	▮▮	▮▮▮
▮	▮▮	▮▮	▮▮	▮▮	▮	▮▮▮

6.6.2   Biocompatibility Testing Overview

The biocompatibility studies comprising this nonclinical safety assessment complied with the International Standard ISO 10993-1 Biological Evaluation of Medical Devices. SCULPTRA is considered to be an implant device in permanent (>30 days) contact with tissue/bone. The safety assessment studies completed for this device included: cytotoxicity, sensitization, irritation, systemic toxicity, sub-chronic toxicity, genotoxicity, implantation, hemocompatibility, and pyrogenicity studies.

The results of these studies indicated that ███████ was well tolerated and is considered to be safe for the intended use in humans. ██████ was found to be neither cytotoxic nor genotoxic and did not induce a sensitization response. ██████ was well tolerated locally (non-irritating), although it was found in one rabbit to be a weak irritant (slight erythema) in the intracutaneous assay. ██████ was non-pyrogenic, did not activate the human complement system and no systemic toxicity was apparent. ████████████████████████████████████ ██████████████████████████ This was the only finding and no other treatment-related changes were observed. This finding was not unexpected as mononuclear macrophages, lymphocytes and foreign body cells are typical tissue responses observed in most commercialized polylactides when the material is implanted subcutaneously.[1] There was no acute inflammation, abscess formation or tissue necrosis correlate with these observations.
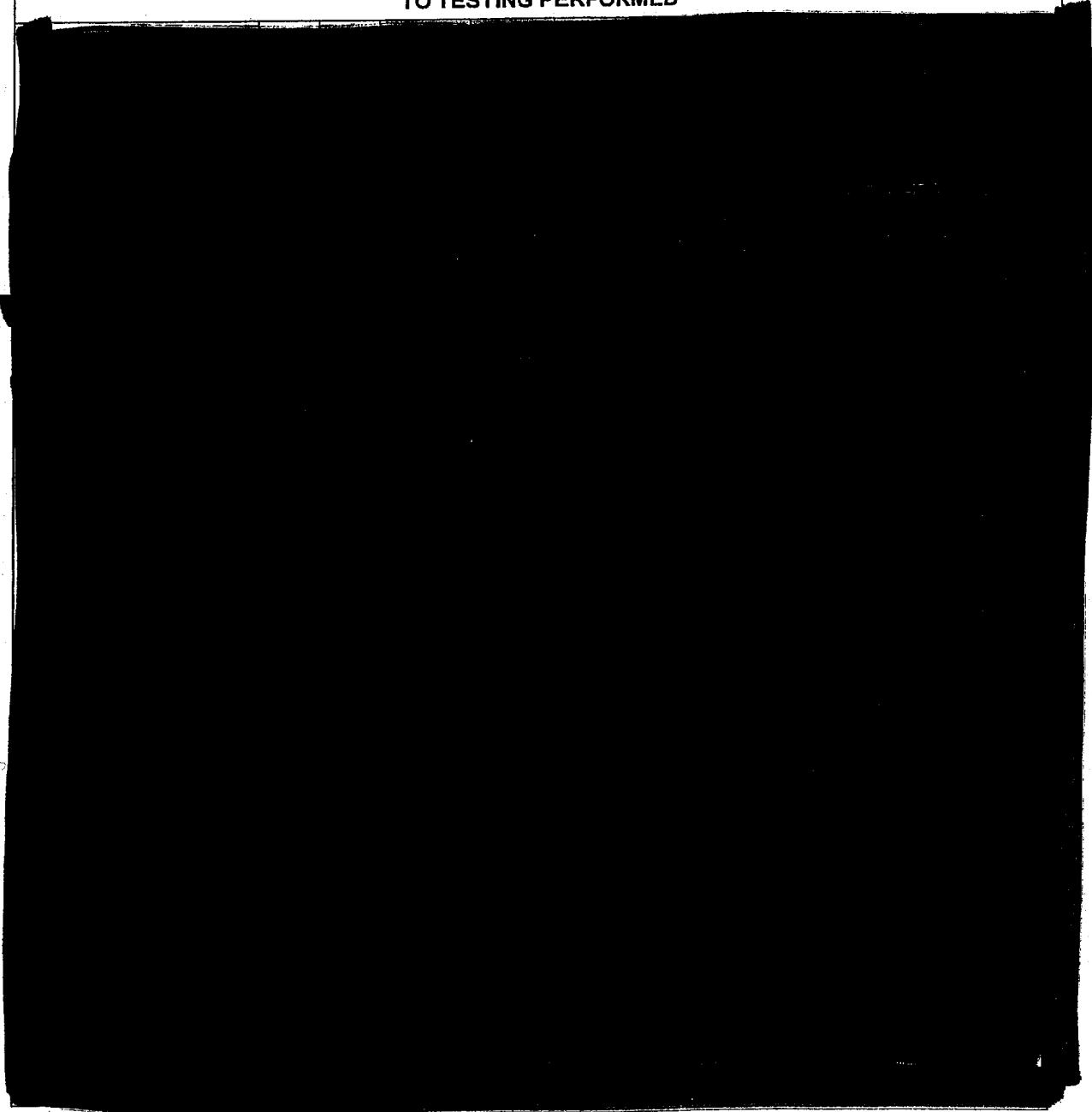
Table 6-10 compares the testing conducted on SCULPTRA with the requirements of the guidance, "Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices" (G95-1, May 1995).

A summary of these studies is provided in Table 6-11 and Section 6.6.4. The study reports are included in Appendix 10.3 Animal Study Nonclinical Reports.

**TABLE 6-10 COMPARISON OF FDA BIOCOMPATIBILITY GUIDANCE
TO TESTING PERFORMED**

6.6.3   Chronic Toxicity and Carcinogenicity Test
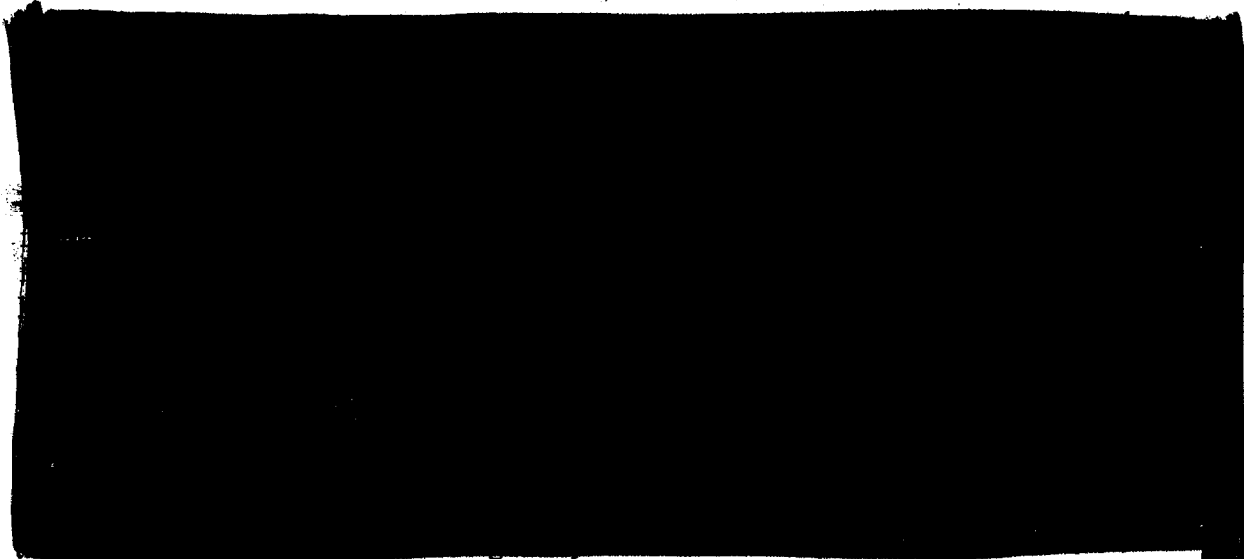
6.6.4   Biocompatibility Test Synopsis

TABLE 6-11 NONCLINICAL TOXICITY STUDIES ACCORDING TO ISO 10993 GUIDELINES

Species (strain) No/Dose Age - Weight Reference	Test Compound (Batch No) Dose Levels Formulation/ Vehicle	Study Design (Laboratory/GLP Status)	Results
Cytotoxicity			

TABLE 6-11 NONCLINICAL TOXICITY STUDIES ACCORDING TO ISO 10993 GUIDELINES (continued)

Species (strain) No/Dose Age - Weight Reference	Test Compound (Batch No) Dose Levels Formulation/ Vehicle	Study Design (Laboratory/GLP Status)	Results
Sensitization			
Intracutaneous (Irritation)			

TABLE 6-11 NONCLINICAL TOXICITY STUDIES ACCORDING TO ISO 10993 GUIDELINES (continued)

Species (strain) No/Dose Age - Weight Reference	Test Compound (Batch No) Dose Levels Formulation/ Vehicle	Study Design (Laboratory/GLP Status)	Results
Systemic toxicity (Acute)			
Sub-chronic toxicity			

TABLE 6-11 NONCLINICAL TOXICITY STUDIES ACCORDING TO ISO 10993 GUIDELINES (continued)

Species (strain) No/Dose Age - Weight Reference	Test Compound (Batch No) Dose Levels Formulation/ Vehicle	Study Design (Laboratory/GLP Status)	Results
Genotoxicity			

TABLE 6-11 NONCLINICAL TOXICITY STUDIES ACCORDING TO ISO 10993 GUIDELINES (continued)

Species (strain) No/Dose Age - Weight Reference	Test Compound (Batch No) Dose Levels Formulation/ Vehicle	Study Design (Laboratory/GLP Status)	Results
Implantation (Local Tolerance)			
Hemocompatibility			
Pyrogenicity			

6.6.5   Summary of Biocompatibility Tests
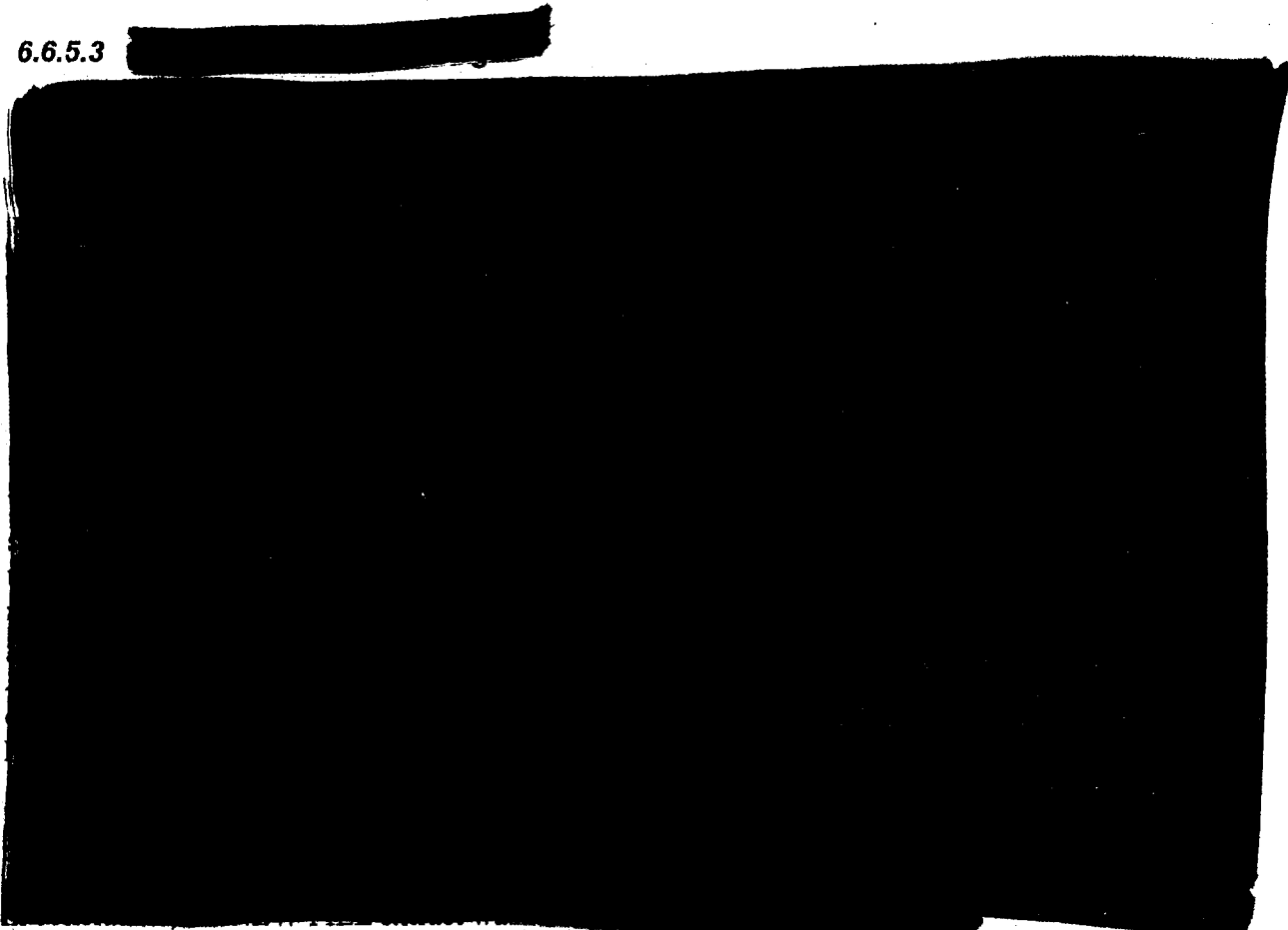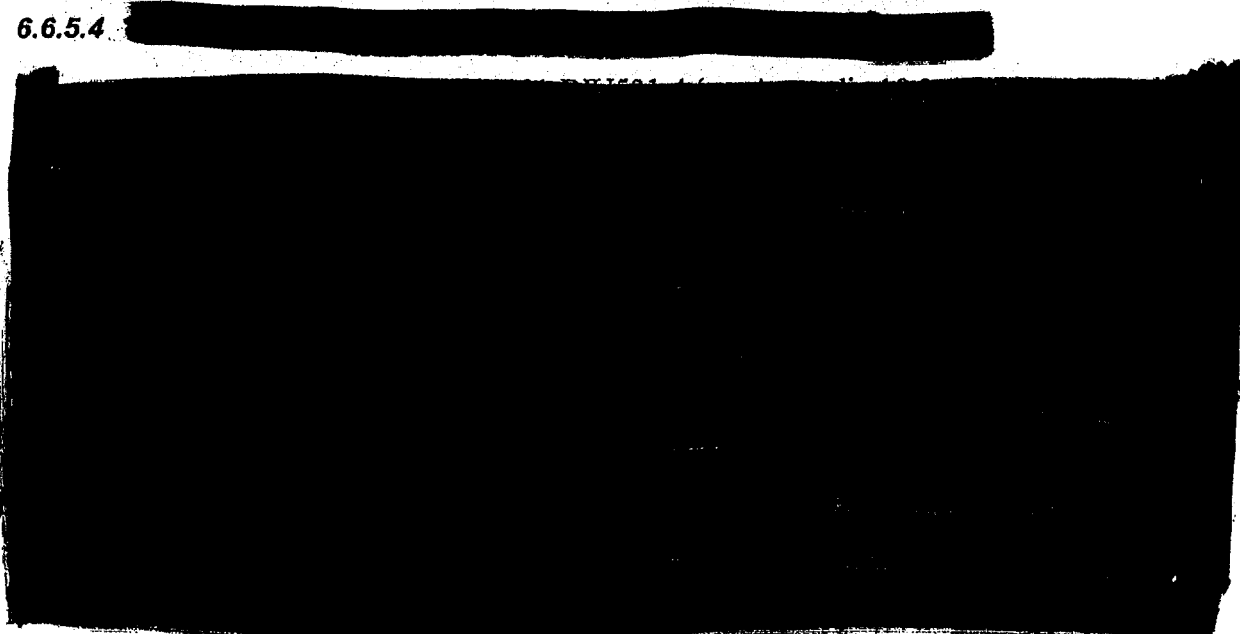
6.6.5.1

6.6.5.2

6.6.5.3

6.6.5.4

6.6.5.5

6.6.5.6

6.6.5.7

6.6.5.8
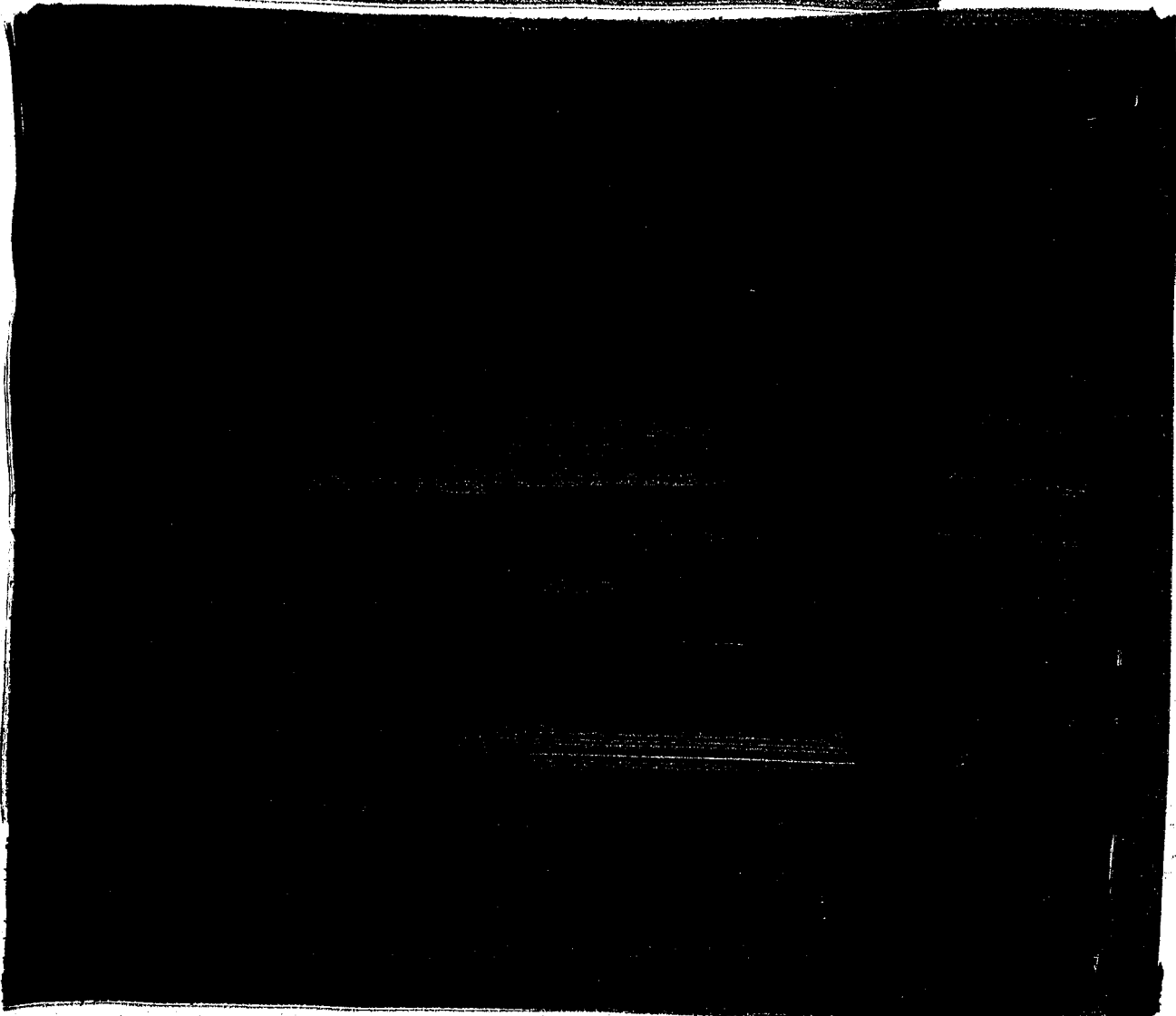
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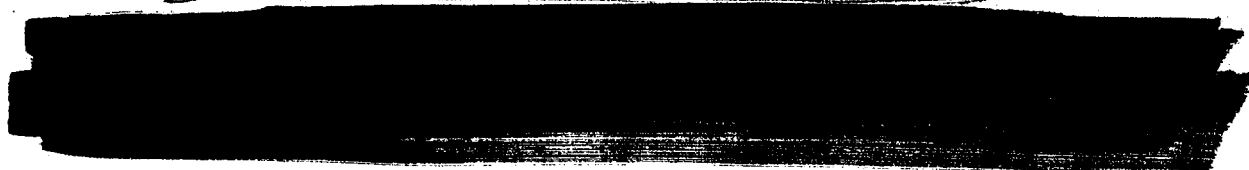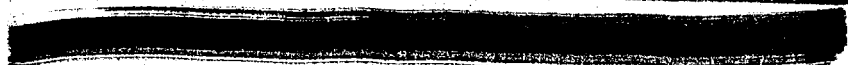
6.6.5.10

6.6.5.11

6.6.5.12
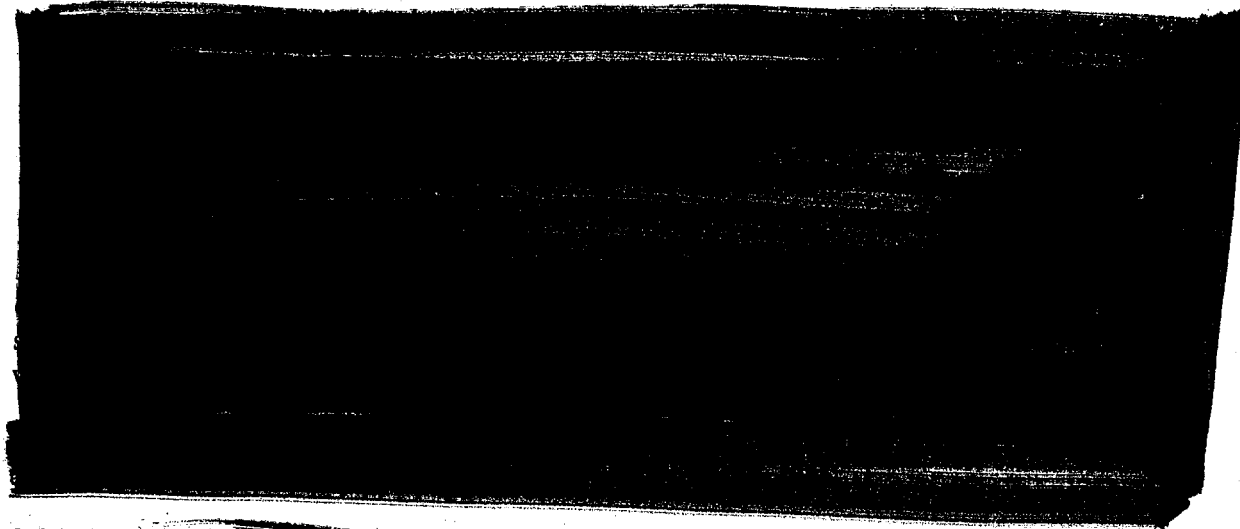
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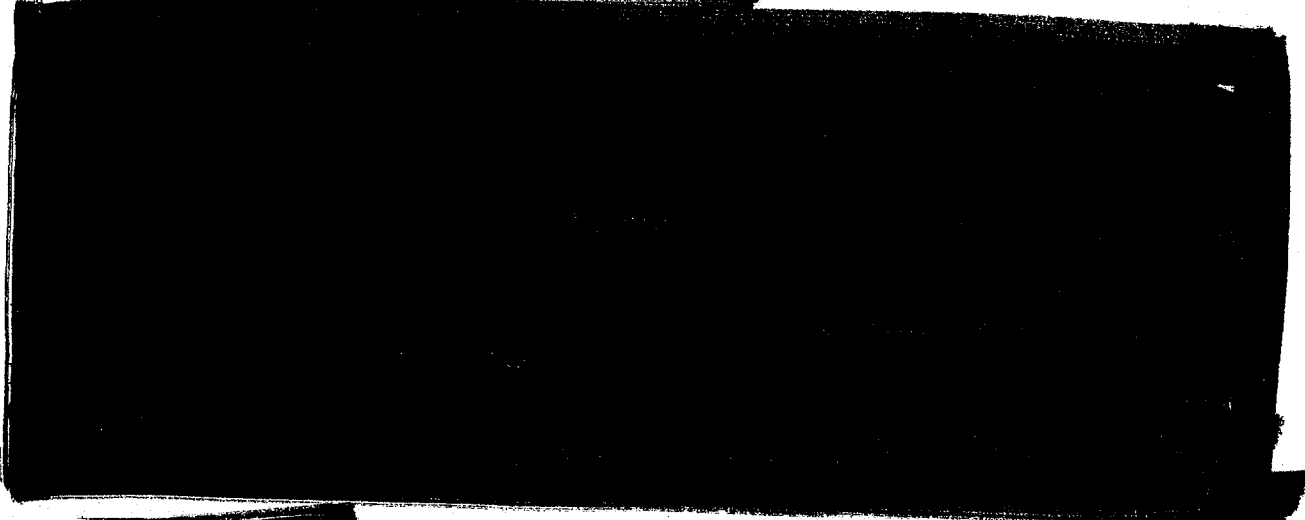
6.7
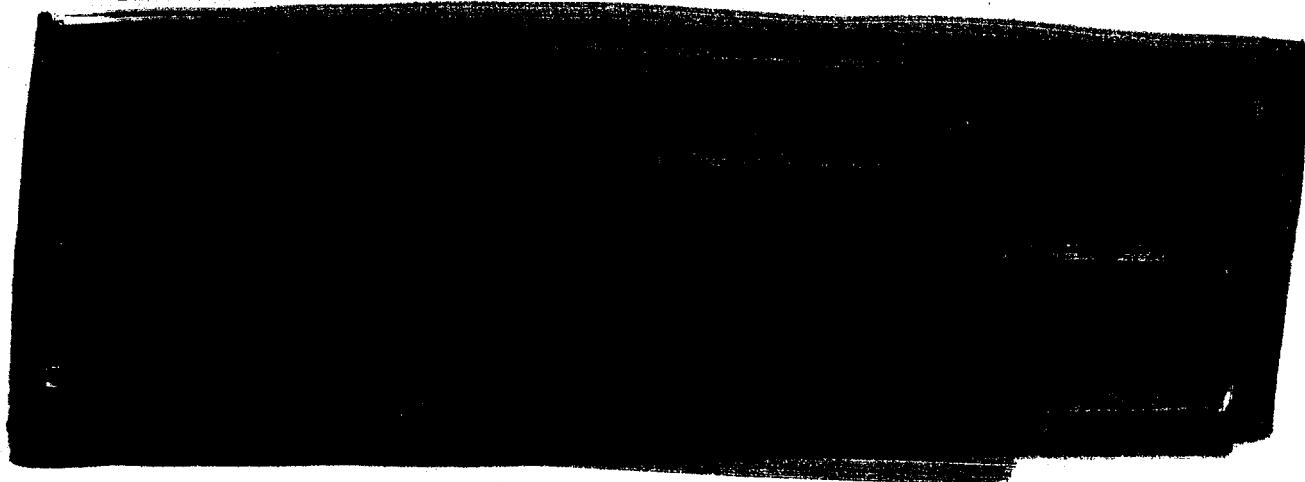
6.8 REFERENCES

The references cited below are provided in Appendix 10.4.

1. Gogolewski, S.; Jovanic, M.; Perren, S.M., *et al.* "Tissue response and *in vivo* degradation of selected polyhydroxyacids: Polylactides (PLA), poly(3-hydroxybutyrate) (PHB) and poly(3-hydroxybutyrate-co-3hydroxyvalerate) (PHB/VA)," *Journal of Biomedical Materials Research*, 1993, v27, p1135-1148.

2. Bergsma, J.E.; de Bruijn, W.C.; Rozema, F.R.; *et al.* "Late degradation tissue response to poly (l-lactide) bone plates and screws," *Biomaterials*, 1995, v1, p25-31.

3. Bergsma, J.E.; Rozema, F.R.; Bos, R.R.M.; *et al.* "Poly (l-lactic) acid implants in repair of defects of the orbital floor. a five-year animal study," *Cells and Materials*, 1994, v4, p31-36.

4. Matsusue, Y.; Hanafusa, S.; Yamamuro, T.; *et al.* "Tissue reaction of bioabsorbable ultra high strength poly (l-lactide) rod," *Clinical Orthopaedics and Related Research*, 1995, n317, p246-253.

6.9 NONCLINICAL BIBLIOGRAPHY

A bibliography of articles relevant to *in vitro* or *in vivo* testing of polylactic acid polymers is provided below.

1. An, K. N.; Chao, E. Y.; Cooney, W. P.; Linscheid, R. L. "Forces in normal and abnormal hand," *Journal of Orthopaedic Research*, 1985, v3, p202-211.

2. Beumer, G. "Biocompatibility of a biodegradable matrix used as a skin substitute: An *in vivo* evaluation," *Journal of Biomedical Materials Research*, 1994, v28, n5, p545-552.

3. Birmingham Polymers, Inc. Brochure: U.S. manufacturers of PLLA and other polymeric materials. Birmingham Polymers, Inc, 756 Tom Martin drive, Birmingham, AL 35211-4467.

4. Brady, J. M.; Cutright, D. E.; Miller, R. A.; *et al.* "Resorption rate, route of elimination, and ultrastructure of the implant site of polylactic acid in the abdominal wall of the rat," *Journal of Biomedical Materials Research*, 1973, v7, p155-166.

5. Cam, D.; Hyon, S. H.; Ikada, Y. "Degradation of high molecular weight poly(L-lactide) in alkaline medium," *Biomaterials*, 1995, v16, n11, p833-843.

6. Celli, A.; Scandola, M. "Thermal properties and physical ageing of poly(L-lactic acid)," *Polymer*, 1992, v33, n13, p2699-2703.

7. Champe, P. C.; and R. A. Harvey. "Glycolysis," in: *Lippincott's Illustrated Reviews: Biochemistry.* 2nd ed. Philadelphia, Pa: J. B. Lippincott Company; 1994, p87-98.

8. Gogolewski, S.; Mainil-Varlet, P.; Nieuwenhuis, P. "Long-term soft tissue reaction to various polylactides and their *in vivo* degradation," *Journal of Material Science: Materials in Medicine,"* 1996, v7, p713-721.

9. Gogolewski, S.; Jovanic, M.; Perren, S. M, *et al.* "Tissue response and *in vivo* degradation of selected polyhydroxyacids: Polylactides (PLA), poly(3-hydroxybutyrate) (PHB) and poly(3-hydroxybutyrate-co-3hydroxyvalerate) (PHB/VA)," *Journal of Biomedical Materials Research*, 1993, v27, p1135-1148.

10. Gupta, M. C.; and V. G. Deshmukh. "Radiation effects on poly(lactic acid)," *Polymer,* July 1983, v24, p827-830.

11. Richeux, F. *In-vivo test: subchronic toxicity study.* Phycher Biodeveloppement; July, 2002, IMP-90J-PH-01/0308.

12. Kronenthal, R. L. "Biodegradable polymers in medicine and surgery," *Polymer Science and Technology*, 1975, v8, p119-137.

13. Lu, L.; Mikos, A. G. "Poly(lactic acid)" in: *Polymer Data Handbook,* Oxford university press, 1999. p627-633.

14. Leenslag, W. J.; Pennings A. J.; Bos, R., *et al.* "Resorbable materials of poly(L-lactide) VII. *in-vivo* and *in vitro* degradation," *Biomaterials*, 1987, v8, p311-314.

15. Lodish, H.; Berk, A.; Zipursky, S. L.; *et al. Molecular cell biology.* 4th ed. New York, NY: W.H. Freeman and Company; 2000, p622-626.

16. Makino, K.; Oshima, H.; Kondo, T. "Mechanism of hydrolytic degradation of poly(L-lactide) microcapsules: effects of pH, ionic strength and buffer concentration," *Journal of Microencapsulation*, 1986, v3, p203-212.

17. Middleton, J. *In vitro degradation of molded poly (l-lactide) parts sterilized by ethylene oxide and gamma irradiation.* Southern BioSystems, Inc.

18. Middleton, J. C.; Kines, P. P.; Roger, A. D. "Degradation of various sterilized lactide, glycolide, and caprolactone polymers,"in: *Biomedical Engineering: Recent Developments.* Medical and Engineering Publishers, Inc.; 2002.

19. Nayak, P. L. "Biodegradable polymers: opportunities and challenges," *J. M. S. - Reviews in Macromolecular Chemistry and Physics*, 1999, C39, n3, p481-505.

20. Rowe, R. C.; Sheskey, P. J.; Weller, P. J. "Aliphatic Polyesters" in: *Handbook of pharmaceutical excipients.* London, Chicago: Pharmaceutical Press; 2003, p19-22.

21. Suming, L.; Garreau, H.; Vert, M. "Structure-property relationships in the case of the degradation of massive poly(L-lactic acids) in aqueous media, *Journal of Materials Science: Materials in Medicine,* 1990, p198-206.

22. Stryer, L. "Glycolysis" in: *Biochemistry.* New York: W. H. Freeman and Company; 1995, p495-498.

23. Van der Elst, M. "The burst phenomenon, an animal model simulating the long-term tissue response on PLLA interlocking nails," *Journal of Biomedical Materials Research,* 1996, v30, p139-143.

24. Williams, D. F. "Enzymic hydrolysis of polylactic acid," *Engineering in Medicine,* 1981, v10, n1, p5-7.

25. Zhu, J. H.; Shen, Z. R.; Wu, L. T.; *et al.* "In-Vitro degradation of polylactide and poly(lactide-co-glycolide) microspheres," *Journal of Applied Polymer Science,* 1991, v43, p2099-2106.

CLINICAL STUDY REPORT

VEGA STUDY

Study of the Impact of Intradermal Poly-L-Lactic Acid Genal Implants on HIV-Positive Patients with Severe Facial Lipoatrophy

Investigators:

Study Site:

Date first patient was enrolled: 22 June 2000
Date last patient completed the study: 13 March 2003

Report type: Original report

INVESTIGATOR STATEMENT:

I certify that, in my capacity as Principal Investigator of this study, I believe to the best of my knowledge, that all data and information submitted in this report are truthful and accurate and that no material fact has been omitted.

NOU 17, 2003
Date

Date of issue: 14 November 2003   VERSION: FINAL

Confidential

STUDY SYNOPSIS

Study short title: VEGA study

Title: Study of the Impact of Intradermal Poly-L-Lactic Acid Genal Implants on HIV-Positive Patients with Severe Facial Lipoatrophy

Investigator, study site:

Study duration and dates: 22 June 2000 to 13 March 2003

Objectives: To evaluate the increase in total cutaneous thickness (TCT) after intradermal poly-L-lactic acid (PLLA) injections in HIV positive patients exhibiting severe lipoatrophy of the face

Study design: Open-label, non-comparative, single center study to determine effects over time.

Number of patients planned: 50

Main Inclusion criteria: HIV positive patients with subcutaneous genal adipose tissue measuring <2 mm by ultrasound. Female patients were not pregnant or lactating. All patients provided a written, informed consent that was previously approved by independent ethics committee (IEC).

Treatment procedures: The majority (86%) of patients received 4 to 5 injection sessions of PLLA (New-Fill®) in the genal area; while 4 (8%) patients received 3 injection sessions, and 3 (6%) patients received 6 injection sessions. The first injection session for PLLA administration was designated as Day 0, then repeated on Days 15 (Week 2), 30 (Week 4) and 45 (Week 6). Additional sessions for PLLA administration were scheduled according to the protocol at the discretion of the investigator.

Effectiveness data: Clinical effectiveness was determined by the percentage of patients who were considered responders [defined as those patients who achieved total cutaneous thickness (TCT) of ≥10 mm]. Additionally, mean TCT was measured over the course of the study by ultrasonography in the genal area at Weeks 8, 24, 48, 72 and 96.

Safety data: Safety was assessed by evaluation of viral load, CD4 cell counts, blood lactic acid, changes in standard blood chemistry parameters, and adverse events (frequency and types).

Quality-of-life (QoL) data: Quality of life (i.e., "overall well-being") was assessed by a Visual Analogue Scale (VAS) at Baseline and at Months 3, 6, 12, 18 and 24.

Statistical procedures: The percentage of responders, the change from baseline in TCT, and QoL was summarized, and analyzed. Paired t-test and the Wilcoxon signed-rank tests were used to analyze TCT and QoL outcomes. Safety data were summarized using descriptive statistics.

Results - Study patients and conduct: Fifty patients were enrolled in this study, and 47 completed the trial. Two patients withdrew from the follow-up period at their own request (after Week 72) and one patient withdrew following a serious adverse event that was determined by the investigator to be unrelated to treatment (after Week 48).

Results - Safety: Forty-eight (96%) of 50 treated patients reported a total of 202 treatment-emergent adverse events (AEs). The most frequently reported AEs were injection site nodule (26, 52%), increased triglycerides (8, 16%), injection site hemorrhage (15, 30%), and diarrhea (6, 12%). Each episode of injection site bruising (3), hemorrhage (15, includes the events hematoma and bleeding), nodules (26, 52%) and edema (2, 4%) was considered by the investigator to be either certainly, probably or possibly related to the New-Fill treatment.

Most of the treatment-emergent adverse events were mild or moderate in intensity. Seventeen (34%) patients reported 25 events of severe intensity. Increased triglycerides, considered to be of severe intensity, were most frequently reported (for 3 patients); all other events of severe intensity were reported only once in this study.

One episode of treatment-related injection site hemorrhage (verbatim term hematoma on right and left cheeks) and one episode of edema was of severe intensity, and the remaining events were either mild or moderate. The aforementioned severe hematoma resolved in 18 days and the edema resolved in 3 days.

A total of 6 (12%) patients experienced one serious adverse event (SAE): anemia folate deficiency, bacterial sepsis, Dupuytren's contracture, lymphoma, skin ulcer of the foot and arteriovenous fistula operation. None of the SAEs were considered related to treatment with PLLA. No deaths were reported in this study.

There were no clinically significant changes from baseline in the CD4 T-cell counts, viral load or blood lactic acid, although a few statistically significant changes were identified at isolated time points. These findings were most likely due to the patients' underlying disease.

Results - Effectiveness: Results are presented for all 50 patients who completed the study. These include the data from 41 patients who authorized access to their medical records and were retrospectively verified to available source documentation.

Every patient treated with the New-Fill device responded positively (minimum increase of 2.2 mm, refer to Table below), and increases above baseline values of mean total cutaneous thickness (TCT) were noted at all time points (Weeks 8, 24, 48, 72 and 96) during the study. The mean increases above the baseline values ranged from 5.2 mm to 7.2 mm over the course of the study (statistically significant, $p < 0.001$, at all time points). The mean TCT increased for up to and including Week 48 measurement time point, and the increases were sustained until the end of the study (Week 96) without any major complications.

7-005b

Total Cutaneous Thickness (mm) by Visit: All Treated Patients							
				Change From Baseline			
Visit	n	Baseline Mean (SD)	Treatment Mean (SD)	Mean (SD)	(Min , Max)	p-value[a]	Responder n (%)
Day 60 (Week 8)[b]	48	3.0 (0.6)	8.2 (1.7)	5.2 (1.7)	(2.2 , 8.7)	<0.001	9 (18.8)
Week 24 (Month 6)	50	3.0 (0.6)	9.4 (1.5)	6.4 (1.6)	(3.0 , 9.1)	<0.001	19 (38.0)
Week 48 (Month 12)	49	3.0 (0.6)	10.2 (1.2)	7.2 (1.3)	(4.3 , 9.6)	<0.001	30 (61.2)
Week 72 (Month 18)	48	3.0 (0.6)	10.2 (1.2)	7.2 (1.3)	(3.5 , 9.3)	<0.001	24 (50.0)
Week 96 (Month 24)	45	3.0 (0.6)	10.0 (1.3)	7.0 (1.4)	(3.9 , 10.2)	<0.001	19 (42.2)

[a]The p-value is based on the paired t-test.
[b]Per Protocol Amendment 1, the Day 45 (Week 6) visit was changed to the Day 60 (Week 8) visit.
Note: Data from patients 2, 9, 20, 27, 32, 36, 39, 40, and 48 are not source-verified but included here.
Data Source: Table 2.1, 28OCT03 – V_FINAL, RESPOND.SAS
  Table 2.2.2, 28OCT03 - V_FINAL, PARA_CHGTCT.SAS

Results - Quality-of-life: A Visual Analogue Scale (VAS) for evaluating "Global Well-Being" assessed the quality of life. This was measured on a scale of 0-10, where 0-4: Unsatisfactory physical and/or emotional state, 5: OK, and 6-10: Satisfactory physical and/or emotional state. Baseline median VAS scores for QoL ranged between 6.1 and 6.7, which relate to the characteristic description of "satisfactory physical and/or emotional state". After treatment, the increase in the median VAS scores ranged between 0.3 and 0.8 over a period of 96 weeks. Statistically significant improvements in QoL (overall well-being) were observed at Months 6 and 12.

Conclusions:

- Facial implants with PLLA (New-Fill®) significantly improve the signs of facial lipoatrophy as demonstrated by increases from baseline in dermal thickness by the Week 8 visit.

- Significant improvements in dermal thickness were sustained throughout the two-year study. These were accompanied by significant increases in patient QoL scores (over well-being) between baseline and Weeks 24, and 48.

- An individualized treatment course of 3 to 6 injection sessions of New-Fill® offers a safe and effective treatment for the signs of facial lipoatrophy that may help alleviate the psychological and social consequences of facial lipoatrophy.

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End-of-text Table (Section 10)

7-010

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LIST OF FIGURES

In-text figures

End-of-text Figures (Section 10)

Figures depicting dermal thickness (as measured by ultrasound) over the course of the study are provided for all 50 individual patients.

7-012

LIST OF LISTINGS (APPENDIX C)

7-013

ABBREVIATIONS AND DEFINITIONS

3TC	Lamivudine, Epivir
ABV	Abacavir, Ziagen
AE	Adverse Event
AZT	Zidovudine, Retrovir
CI	Confidence interval
CRF	Case report form
d4T	Stavudine, Zerit
DDC	Zalcitabine, Hivid
DDI	Didanosine, Videx
FDA	Food and Drug Administration
EHMDS	European Harmonized Medical Device Standards Agency
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HIV	Human immunodeficiency virus
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
INSERM	Institut National Français de Recherché Médicale
MedDRA	Medical Dictionary for Regulatory Activities
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitors
NRTI	Nucleoside Reverse Transcriptase Inhibitors
nos	Not otherwise specified
PI	Protease Inhibitor
PLLA	Poly-L-lactic acid
QoL	Quality of life
SAE	Serious adverse event
SD	Standard Deviation
SDV	Source document verification
TCT	Total cutaneous thickness
UADE	Unanticipated adverse device effects
VAS	Visual analog scale

7-014

1. INTRODUCTION

Recent progress in antiretroviral therapy combining reverse transcriptase and protease inhibitors has resulted in strongly inhibited human immunodeficiency virus (HIV) replication in many patients. This has led to an increase in CD4 counts, which is responsible for a widespread reduction in opportunistic infections and a longer survival rate[1].

However, many publications and clinical observations point toward the occurrence of a lipodystrophic syndrome that is affecting long-term therapy in many of these patients. This partial or generalized syndrome is characterized by a modification in the distribution of subcutaneous and perivisceral adipose tissue, possibly linked to anomalies in the lipid-carbohydrate balance, mainly leading to increased triglycerides and the appearance of insulin resistance[2-7].

Although there is at the present no consensus of opinion for defining lipodystrophy, it is most often described in three clinical forms: lipoatrophy, central adiposity, and a mixed form of peripheral lipoatrophy and central adiposity. Lipoatrophy is characterized by a loss of the fat pads of Bichat, atrophy of retro-orbital adipose tissue, atrophy of subcutaneous adipose tissue in the limbs with thinning of the arms, thighs and buttocks, and related venomegaly. Central adiposity is characterized by increased abdominal and breast volume, and the possible appearance of excessive subcutaneous fat deposits on the rear base of the neck, the so-called "buffalo hump". This clinical form may be associated with blood anomalies involving lipid and carbohydrate metabolism[8,9].

The most recent studies show the prevalence of lipodystrophy to be around 60% in HIV-positive patients undergoing antiretroviral treatment[10-12]. On the other hand, prevalence of the different clinical forms varies from one study to another. An Australian study estimates central adiposity to be at 14%[12], while two French studies (APROCO[10] and LIPOSUD[11]) show it ranges from 30% to 40%. The mixed form is estimated at 55% in a study by Cooper, as compared to 25% and 32% in the APROCO and LIPOSUD studies. Lastly, the frequency of lipoatrophies is similar at around 30% in all three of these studies.

Although it has yet to be clearly established, there appears to be a link between the clinical form and the nature of the antiretroviral therapy. Therefore patients treated with protease inhibitors likely develop a central form more frequently, most often associated with carbohydrate-lipid anomalies[10]. Varying factors are also associated with a greater susceptibility to develop lipodystrophy: age, sex, ethnic origin, duration of the HIV infection, duration of exposure to treatment, namely to d4T, and changes in body mass index[5,13,14].

The importance of lipoatrophy, especially when it affects the face, can have extreme psychological and social ramifications. In effect, once the panniculus adiposus has been reached, it may lead to an evident, deep-seated emaciation of the face.

For an outside observer, these signs may suggest a serious and progressive pathology, comprising a major element of ill being for those who are affected. Although changes in the legs and arms can be easily hidden, those of the face cannot.

Lacking any clear physio-pathogenic explanation for these anomalies, and realizing that there is no etiological treatment of clearly proven efficacy, an attempt at a palliative symptomatic therapeutic approach to relieve patients is indicated. In effect, any change in the application of proposed antiretroviral treatments would risk altering the immuno-virological prognosis for patients in this situation.

Among various palliative cosmetic approaches aimed at filling the subcutaneous adipose space, four major approaches are described here. These include: autograft, non-biodegradable implants, biodegradable implants, and a unique alternative of New-Fill® injection.

Autograft, Colman's method for autografting adipose cells consists of removing adipocytes from abdominal subcutaneous tissue. After ultracentrifuging, these cells are reimplanted under the skin in the lipoatrophied area. However, this is a major procedure, requiring general anesthesia for puncturing the abdominal adipose tissue. Moreover, the reimplanted tissue could disappear under a kinetic situation similar to that constituting the original lipoatrophy. Lastly, and above all, there may be no benefit to some patients lacking sufficient abdominal panniculus adiposus.

Non-biodegradable synthetic implants, particularly silicone, have the inconvenience of possible allergic reactions—immediate or delayed—and the creation of inflammatory granulomas, with possible rejection[15].

Other techniques use **biodegradable implants**. They may be of animal origin, such as collagen, leading to the risk of allergic reactions in 2-3% of cases, or of biological origin, such as hyaluronic acid, which is quite rapidly reabsorbed in a matter of weeks or months[16-19].

New-Fill® is a poly-L-lactic acid (PLLA) hydrogel, a biocompatible, biodegradable, and immunologically inert synthetic polymer. PLLA has been used for many years in numerous therapeutic applications as a resorbable suture material in ophthalmologic, neurological, and thoracoabdominal surgery. In traumatology, materials for osteosynthesis and ligament repair have been made from this chemical. Lastly, PLLA is widely used in maxillofacial surgery, in periodontology and stomatology, mainly as a support for tissue regeneration in treating bone defects[20-23].

The replacement of subcutaneous volume due to the loss of adipose tissue, observed in lipoatrophy syndrome, is a possible indication for these cutaneous filling procedures. A potential mechanism of action of New-Fill® may include a direct thickening of skin tissue owing to its own volume, and indirectly over time by PLLA causing a local fibroblastic and neocollagenous response reaction.

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Among the many questions yet to be answered about subcutaneous implants in lipoatrophic HIV-positive patients, the most important ones relate to the immediate tolerance for the technique used, duration of effectiveness, and potential long-term local toxicity in the skin that accepts any implants.

Accordingly, the current study of 50 patients who had severe lipoatrophy of the face evaluated the effects of New-Fill® implants in the cheeks (consisting of 3 or more injections spaced apart by more than 2 weeks). Patients were monitored for up to 24 months to assess tolerance, safety, and durability of beneficial effects. The study was conducted independently at a single center by physicians at the ██ Commercially available product was used for the trial.

All available data were monitored and verified retrospectively after obtaining authorization from 41 of 50 patients entered into the study by a contract research organization ████████████. For the nine patients who did not give consent (████████████████████████████) anonymous, unverified data were included in the analysis. Results were also analyzed using only the 41 patients with source data verification completed to determine the impact of unverified data.

2. IDE CONDUCT

2.1 INDICATION OF IDE STATUS

This study was run independently by the clinical investigator in ████ and was not conducted under a United States Investigational Device Exemption (IDE).

2.2 APPLICABILITY OF FOREIGN DATA TO US POPULATION

Similar antiretroviral treatment is used for the treatment of HIV in Europe and the US. Since there appears to be a link between antiretroviral therapy and lipodystrophy, the results of this study would have application both in Europe and in the US.

2.3 ETHICS

This study was conducted according to ████████████, which requires approval of the study by an independent ethics committee and obtaining written informed consent from participating patients.

2.3.1 Independent ethics committee

The protocol was submitted to ██ to

Committee Members: ████████████ Chairperson
Nurse
Epidemiologist
Pharmacist
Hospital Psychologist
Biochemist
Pharmacologist
General Practitioner

Amendments 1 and 2 were reviewed and given a favorable opinion on November 8, 2000.

2.3.2 Patient Information and Informed consent

Patient's informed consent was obtained prior to the conduct of any study related procedures. Patient 11 signed the informed consent on June 30, 2000 but had study procedures (clinical exam, and facial ultrasound) completed on June 29, 2000. However, this patient did not have the first injection session until July 1, 2000.

After the study was clinically completed, an "Informed and voluntary consent to the collection, processing and usage of personal data" form was signed by 41 of 50 patients authorizing the verification and release of the data obtained in this study to Dermik Laboratories (a subsidiary of Aventis), for use in regulatory applications for the product. Anonymous, unverified data for the 9 remaining patients were included in the analysis.

Appendix A.1.4 contains copies of both informed consent documents.

2.4 PROTOCOL AMENDMENTS AND ADMINISTRATIVE CHANGES

Two amendments were made to the protocol; both amendments were considered with favorable opinion (i.e., approved) by the Independent Ethics Committee (IEC) on November 8, 2000.

Amendment 1

Based upon initial experience with the first 16 patients who received New-Fill® treatment as originally described in the protocol, a fourth bilateral injection was included. The protocol was amended to standardize the fourth injection. Accordingly, an optional fifth injection was allowed for patients who had received four injections of New-Fill, and whose dermis was found to be of less than 8 mm in thickness. This amendment also affected the scheduling of ultrasound measurements, by changing the assessment day from Day 45 to Day 60.

Amendment 2

Amendment 2 provided for the scheduling of follow-up photographs. Photographs were then obtained at Screening, and Months 6, 12, 18 and 24.

2.5 ADMINISTRATIVE STRUCTURE

Details of the personnel who initiated and supervised this study, and their role in the study, are given below:

- ██
- ██
- ██
- ██
- ██
- ██
- ██
- ██

All records for this study are located at ████████████████████

3. CLINICAL STUDY METHODS

3.1 OBJECTIVE

This study evaluated the effects of poly-L-lactic acid (PLLA, New-Fill®) injections in the genal (i.e., cheek) areas of HIV-positive patients with severe facial lipoatrophy receiving antiretroviral treatment. Safety of such implants, the extent and durability of beneficial effects were measured in all treated and enrolled patients.

3.2 STUDY DESIGN

This was an open-label, non-comparative, single-center study of 50 HIV-positive patients who received injections of PLLA in the depressed genal areas of the face. There was only one treatment

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group. All patients received 3 to 6 injection sessions in the mid-dermis of the treatment area. All 50 patients received at least 3 injection sessions at approximately 15-day intervals. A fourth and possibly a fifth injection session was permitted; the latter was included if dermal thickness in the genal area remained less than 8 mm. Additionally, in the case of extreme temporal atrophy, supplementary injections were permitted in other facial areas. Only the genal areas were considered for effectiveness.

3.3   CLINICAL ENDPOINTS AND MEASUREMENTS

- Change from baseline in total cutaneous thickness (TCT).
- Evaluation of the "Global Well-Being" aspect of quality of life (QoL) as measured on a Visual Analog Scale (VAS).
- Change in the viral load, CD4 cell count and levels of blood lactic acid.
- Change in standard biology parameters (e.g. blood chemistry).
- Adverse events.

3.4   TIME COURSE OF OBSERVATIONS/FOLLOW-UP

HIV positive patients with marked facial lipoatrophy, who had a genal subcutaneous adipose tissue thickness of less than 2 mm, were screened for eligibility 2 weeks prior to enrollment in this study (i.e., Day – 14).

On Day 0 of the study, eligible patients received bilateral facial intradermal injections of up to 0.15 g (3 ml) of PLLA (New-Fill®) in each cheek.

These injections were repeated on Days 15 (Week 2), 30 (Week 4), and 45 (Week 6) after the initial treatment. If skin thickness was less than 8 mm at Day 60 (Week 8), patients could receive additional injections of PLLA. Further injections were permitted during the study away from the genal area at the treating physicians discretion.

A summary of study events inclusive of a schedule for injections is shown in Figure 1: Study Schedule Summary below.

Figure 1: Study Schedule Summary
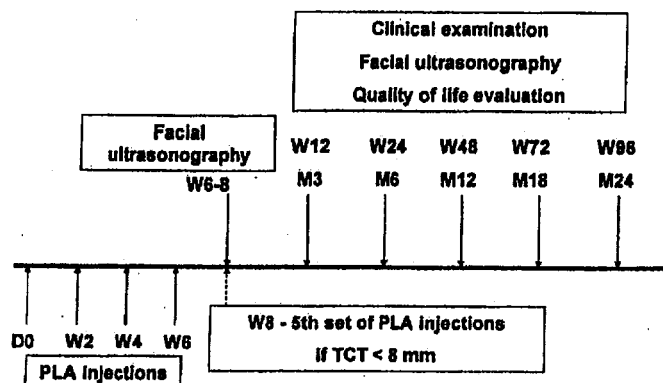
3.5   COLLECTION OF ADVERSE EVENTS

At each visit a clinical examination was conducted and adverse events were recorded on a "Clinical and/or Biological Undesirable Events" case report form (CRF) page.

For any adverse events deemed by the Investigator to be serious, additional data were collected on a "Severe Undesirable Events – Additional Data" CRF page.

3.6   DURATION OF STUDY – START TO FINISH

Patients were monitored for 96 weeks (2 years) after the first treatment session of PLLA on Day 0. The patient enrollment began in June 2000 and the last patient completed the follow-up phase in March 2003.

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3.7   CLINICAL SIGNIFICANCE

Clinical effectiveness was determined by the percentage of patients who were considered responders [defined as those patients who achieved total cutaneous thickness (TCT) of ≥ 10 mm]. Additionally, mean TCT was measured over the course of the study by ultrasonography in the genal area at Weeks 8, 24, 48, 72 and 96. This value of 10 mm was arbitrarily chosen by evaluating a few non-HIV-infected individuals.   The change from baseline in TCT was also evaluated over the course of this study.

3.8   STATISTICAL HYPOTHESIS

3.8.1 Effectiveness Hypothesis

Although not specifically stated in the protocol, based upon the design of the study the null hypotheses are considered: 1) there are no changes in TCT values from baseline, and 2) there are less than 60% responders (TCT ≥ 10mm) at the Month 6 visit. If statistically significant changes are observed in the TCT changes from baseline, the null hypothesis should be rejected.

3.8.2 Evaluation of Safety Results

The safety of the study treatment was evaluated by analysis of the adverse events and laboratory values reported in this study.

3.9   SAMPLE SIZE CALCULATION FOR NUMBER OF PATIENTS AND ITS BASIS

Sample size was based upon the assumption that the percentage of patients with satisfactory results ("responder" with a mean TCT ≥ 10 mm) after 6 months would be 80%, and that the number of responders would be significantly higher than 60%. With an α risk of 0.05 and 90% power based on a chi-square test, sample size calculations determined that 50 eligible patients were required to enter this study.

3.10   STUDY PATIENT POPULATION

3.10.1 Number of Patients

Of the total 54 patients screened, 50 eligible patients were enrolled into the trial.

3.10.2 Inclusion Criteria

Patients meeting all of the following criteria were to be considered for enrollment into the study:

1. Age >18 years old.
2. HIV-positive.
3. Plasma HIV viral load <5000 copies/ml for more than 3 months.
4. Current antiretroviral treatment commencing at least 3 months before screening for entry into the trial.
5. Antiretroviral treatment commencing at least 3 years before screening for entry into the trial.
6. Subcutaneous genal adipose tissue measuring <2 mm by ultrasound.

3.10.3 Exclusion Criteria

Patients meeting any of the following criteria were not to be included in the study:

1. Clinical illness under investigation or in the acute treatment phase.
2. Extensive travel time to the study or a long trip foreseen during the first 2 months of study.
3. Patient refusing treatment and/or with irregular follow-up.
4. Dermatological disease of the face incompatible with tested treatment.
5. Cutaneous Kaposi's sarcoma of face.
6. Injection of filler material into area during the previous 6 months.
7. Concurrent herpes labialis.
8. Concomitant treatment with interferon.
9. Pregnant or nursing women.

3.11 STUDY PROCEDURES AND SCHEDULE

3.11.1 Description of Study Visits

A summary of the determinations performed at each study visit is provided in Table 1, at the end of this section.

Patients attended the clinic for a screening visit approximately 2 weeks before administration of the first session of PLLA. At the screening visit, demographic information, morphological changes in fat distribution, and concurrent medication were recorded. A clinical examination was carried out and blood samples were taken for measurement of standard hematological and biochemical variables, lactate levels, CD4 T-lymphocyte counts, and viral load (HIV-RNA).

Ultrasound measurements were performed to assess facial skin thickness prior to treatment; photographs were taken for comparative visual evaluation of the efficacy of the PLLA injections; and the patient completed a QoL questionnaire.

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The first injection session of PLLA was administered on Day 0. The injection sessions were repeated approximately every two weeks up to Day 45 or 60 [note that Day 45 and Day 60 (Months 2 to 3) may be used interchangeably due to Amendment 1]. If skin thickness was less than 8 mm at Day 60 (Week 8), patients received an additional injection session of PLLA. However, the actual days between injection sessions varied for patients.

Patients were evaluated by clinical examinations at screening, and at Month 3, Month 6, Month 12, Month 18, and Month 24 of this study. Facial photography including front and side views was performed at baseline, Week 6-8, Month 3, Month 6, Month 12, Month 18, and Month 24. Ultrasound measurements were taken at baseline, Week 6-8, Month 3, Month 6, Month 12, Month 18 and Month 24. Details of concurrent medication and adverse events were recorded at all visits, and laboratory samples were taken for measurement of biochemical parameters at baseline, Week 6-8, Month 3, Month 6, Month 12, Month 18 and Month 24. At baseline, and at Month 3, 6, 12, 18, and 24, a QoL questionnaire was completed by the patient.

Table 1: Schedule of Assessments

Study Event or Measurement	Time points in Days or Months (Weeks)										
	Screening D -14(-2)	Baseline 0	D 15 (2)	D 30 (4)	D 45 (6)	D 60 (8)	M 3 (12)	M 6 (24)	M 12 (48)	M 18 (72)	M 24 (96)
Consent	✓										
Lactate, HIV RNA & CD4	✓						✓	✓ᵃ	✓	✓	✓
Clinical examination	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Routine Laboratory Tests	✓				✓ᵇ	✓ᵇ	✓	✓	✓	✓	✓
Facial Ultrasound	✓				✓ᵇ	✓ᵇ		✓	✓	✓	✓
Photographs	✓							✓	✓	✓	✓
Quality of Lifeᶜ	✓						✓	✓	✓	✓	✓
Injection Sessions		✓	✓	✓	✓ᵈ	✓ᵈ					
Adverse Events		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medications		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

a: Lactate determination, only at Month 6.
b: Assessments changed from Week 6 (D45) to Week 8 (D60) per Amendment 1.
c: QoL assessment was meant to be collected at Day 45/60, but it was not collected until Month 3 or 6.
d: Additional injection(s), if skin thickness was < 8 mm per Amendment 1.
Abbreviations: D = day, M = month, HIV = human immunodeficiency virus, RNA = ribonucleic acid.

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3.11.2 Methods

3.11.2.1 Doppler Ultrasound

Doppler ultrasound was used for radiological evaluation of the epidermis, dermis and subcutaneous panniculus adiposus of the facial tissue, to assess dermal thickness and neovascularization.

The ultrasound technician used a digital multi-frequencies 7.5 to 13 megahertz transducer and a 7-megahertz color Doppler (Logiq 7, General Electric, Milwaukee, Wisconsin).

The genal area was examined by placing bilateral marks in front of the masseter, on the center of the buccinator muscle, and on the zygomatic bone. To ensure that a clear, reproducible, easily interpretable image was obtained of the three components of the cutaneous tissue, the ultrasound technician was required to apply at least 1 cm of gel to the area to be examined; scan as lightly as possible over the area being examined to avoid causing pressure distortion of the skin; and to record images for each genal area.

To ensure consistency between readings, ultrasound recordings were performed by only one person, ▮▮▮▮▮▮ using the same apparatus throughout the study.

During the procedure:

- cutaneous depressions were examined in the genal area,
- the appearance and changes in neovascularisation were recorded using Doppler ultrasound.

Images obtained from ultrasound scanning were stored on computerized media. Printouts are retained at the hospital in the patient's records.

Although the temporal areas were to be assessed per the protocol, only the genal areas were assessed during the study. Note that the minimum and maximum dermal thickness were captured at each ultrasound measurement recorded for each side.

3.11.2.2 Quality of Life (Overall well-being)

Patients assessed QoL by placing a horizontal mark on a vertical scale on which the numbers 0, 5 and 10 were pre-printed. On the scale, 0 to 4 was noted to be an "Unsatisfactory physical and/or emotional state"; 5 was noted as being "OK"; and 6 to 10 was noted as being in a "Satisfactory physical and/or emotional state". Note: These were not validated measurements. The data are included in Listing 21 (Appendix C).

3.11.2.3 Clinical Examination

Weight and height were recorded and Karnofsky's index assessed. An examination was performed and the cardiac, pulmonary, digestive, neurological and cutaneous systems were assessed. Any abnormalities of these systems were noted. These data are included in Listing 12 (Appendix C).

The presence or absence of the following lipodystrophy-associated morphological modifications were noted at screening (refer to Listing 2 of Appendix C):

- Loss of Bichat's fat pads.
- Atrophy of upper extremities.
- Atrophy of lower extremities.
- Modification of venous network.
- Buffalo hump.
- Increase in breast volume.
- Increase in abdominal circumference.

Data were collected on historical (see Listing 4) and current antiretroviral therapy (see Listing 26) and concomitant medications (see Listing 25), Appendix C.

3.11.2.4 Adverse Events (AEs) and Serious Adverse Events (SAEs)

Any events, effects, and untoward changes reported by the patient or noted by the investigator during the clinical examination were recorded as adverse events on the designated "Clinical and/or Biological Undesirable Events" page of the CRF. During the detailed verification process and retrospective review of data, a number of treatment procedure associated events were identified and subsequently added to the adverse event listings. However, due to either incomplete or limited details of initial observations in the records at the site, a number of these AEs could not be assigned intensity criteria. Therefore, there are 15 treatment-related adverse events without an intensity noted.

For any AE that was deemed by the investigator to be a serious AE (SAE), additional data were collected on a designated "Severe Undesirable Events – Additional Data" page of the CRF.

3.12 USE OF DEVICE

3.12.1 Device Description

New-Fill® is a skin implant in the form of a sterile apyrogenic suspension, which is reconstituted from a sterile dry powder by the addition of sterile water for injection. This suspension contains microparticles of poly-L-lactic acid, the crystalline form of PLLA. This synthetic polymer is biocompatible, biodegradable, and immunologically inert.

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To reconstitute the product, slowly add 3ml of sterile water for injection to the dry powder and let it stand for at least 20 minutes (do not shake) to ensure that the powder dissolves. Shake until a homogeneous translucent suspension is obtained. It is then ready for use. [New-Fill® (Package Insert) Luxembourg: Biotech Industry S.A.; 2002.]

3.12.2 Treatment Procedures

For each course of treatment, one vial of New-Fill® was reconstituted by the addition of 3 ml of sterile water for injection. Local anesthesia (with Xylocaine or EMLA) was utilized for pain reduction as needed.

3.12.2.1 Frequency of Injections

Injections were repeated approximately every two weeks until each patient had received a minimum of 3 injection sessions (a fourth injection session was then added per Amendment 1). A fifth injection session was offered if the skin thickness was less than 8 mm at approximately 15 days after the fourth injection. If major temporal atrophy was present, additional injections were offered at separate times in areas other than the cheek area.

3.12.2.2 Treatment Administration

On treatment days, generally 3 ml of the reconstituted PLLA hydrogel was injected intradermally into multiple points of the genal (cheek) treatment area on each side of the face. The quantity of solution injected depended upon the severity of the facial depression. Following injection, the skin was massaged to evenly distribute the product.

3.13 WITHDRAWAL AND REPLACEMENT PROCEDURES

There were no replacement procedures for patients who withdrew consent or prematurely discontinued from the study.

3.14 QUALITY ASSURANCE AND QUALITY CONTROL

3.14.1 Data quality assurance

Complete hospital records were kept for each patient, as appropriate in routine clinical practice. Patients had voluntarily signed and provided an approved patient's consent form prior to enrollment in this study, as defined in the protocol.

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An independent biostatistics group at the hospital investigative site single-entered data from the CRFs into a database, (INSERM). Analyses were subsequently performed by the ██████ statistician, and a preliminary report was generated for poster presentation (see Appendix A.6).

████████████████ (on behalf of Dermik) conducted a retrospective evaluation of the data. The investigator's original database was transferred to ███████. The contents of the database were verified to the source records ████████████████████████████████████ After an extensive verification process by clinical monitors, the database was prepared for further analyses, with generation of various tabulations, listings and summary outputs by ████████ ████████ These outputs were used in the writing of this clinical study report. Additional details can be found in the Data Management Plan, Appendix A.4.3.

3.14.2 Monitoring and auditing

Since this study was not originally intended for registration purposes, the trial was not externally monitored during the conduct of the study. However, for ██████ patients who gave their consent for review of their medical records, retrospective verification against the available source documentation was performed by the contract research organization, the ███████████ Data discrepancies were corrected using standard data clarification forms consistent with the procedures established by ████████████ During this retrospective monitoring of the study, the majority of the data was available for verification.

During the review by the ████████████, source document verification (SDV) was performed on key efficacy and safety data. The hospital records were reviewed with particular attention to efficacy data (i.e., ultrasounds), and safety data (i.e., adverse events, serious adverse events, and laboratory studies). The data were subsequently analyzed by the ███████████ using the queried and validated data in a manner that was consistent with the investigator's original analyses.

All records relating to the treatment administrations were reviewed at the hospital site, where all documentation of the injection records are retained.

A quality control check of the database (100%) was performed prior to database lock by ███████████ ██████ to ensure consistency of the data. In addition, an audit of the site was performed by ██████ ███████████████████████ Audit Certificate is provided in Appendix A.4.4.

4. STATISTICAL AND ANALYTICAL PROCEDURES

4.1 STUDY VARIABLES

The study variables for determining New-Fill® effectiveness and safety were as follows.

Effectiveness

- Change from baseline in total cutaneous thickness (TCT) measured by ultrasound.
- Percent (%) of responders (TCT ≥ 10 mm) as measured by ultrasound.
- Evaluation of the "Global Well-Being" aspect of quality of life (QoL) as measured on a Visual Analog Scale (VAS).

Safety

- Frequency and types of AEs.
- Change in standard biology parameters (e.g. blood chemistry) and other laboratory parameters (viral load, CD4 cell count, and blood lactic acid levels).

4.2 STATISTICAL METHODOLOGY

The ███████████retrospectively analyzed individual patient data in order to duplicate the original analyses of the investigators using the queried and verified data sets. An "Informed and voluntary consent to the collection, processing and usage of personal data" form was signed by 41 of the 50 patients authorizing release of the data obtained in this study to Dermik Laboratories, for use in a regulatory application for the product. Thus, ██████atients who gave consent were monitored and verified retrospectively after obtaining authorization. For those patients, whose data-use consent forms were not obtained (due to unavailability of patients), included patient██████████████ ████████████owever, the unverified and anonymous data from these patients are included in the analysis.

Data were analyzed using SAS statistical software. All statistical tests were two-sided with a significance level of 0.05.

4.2.1 Baseline Information

Baseline continuous parameters such as age were summarized by the number of patients with non-missing values (n), the mean and standard deviation (SD), the median, the minimum value, and the maximum value. Categorical parameters such as gender were summarized by the number and percentage of patients in each category.

4.2.2 Efficacy Analysis

4.2.2.1 Total Cutaneous Thickness Calculations

Each patient had two skin thickness measurements on each side and one adipose tissue thickness measurement on each side. In many cases the adipose tissue thickness was not measurable and in those cases, the missing value was set to zero. The radiologist carried forward the adipose measurements from baseline due to technical reasons. Total cutaneous thickness (TCT) was

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calculated by adding the adipose tissue thickness to the skin thickness for each side of the face. This gave four possible measurements per patient. The four measurements were then averaged to give a single mean TCT measurement for each patient. In the cases in which the second skin thickness measurements were not done or were missing, the average of the two TCT calculations was used as the TCT result for that patient.

Data were normally distributed; therefore mean values are presented (median values are also provided).

4.2.2.2 Visual Analog Scale Evaluations

The VAS for evaluating "Global Well-Being" assessed patient quality of life. This was measured on a scale of 0-10, where 0-4 = Unsatisfactory physical and/or emotional state, 5 = OK, and 6-10 = Satisfactory physical and/or emotional state.

Data were not normally distributed; so median values are presented (and mean values are also provided).

4.2.2.3 Responder Rate Analysis

Responder rates were based on the percentage of patients with mean total cutaneous skin thickness of 10 mm or greater at each visit. The number of patients with non-missing values was displayed along with the number and percentage of responders. A 95% exact binomial confidence interval (CI) was provided for the responder rate at each visit.

The data for total cutaneous thickness was shown to be normally distributed.

An analysis of the Week 24 responder rate was planned in the protocol to show that the responder rate at that time point was significantly higher than 60%. This Chi-Square Test was not performed due to the fact that the actual response rate for this time point was less than the 60% threshold.

4.2.3 Safety Analysis

The laboratory parameters, CD4 (mm^3), Viral Load (log_{10} copies/ml), and blood lactic acid (mmol/l) were summarized. Displayed in the table for each visit were the number of patients with non-missing values, the baseline mean, the treatment mean, the mean change and standard deviation, the minimum and maximum change from baseline values, and the p-value based on the paired t-test. As in the baseline summary, viral load measurements equaling zero were changed to 0.0001 (10^{-4}) and were transformed using the base 10 logarithm.

Treatment-emergent adverse events (TEAEs) were recorded by the investigator, and displayed in the listings (Listing 23.1) as well as the summary tables (Tables 3.2, 3.3, 3.4, 3.5, and 3.6) by system organ class and MedDRA preferred term. For the determinations of most frequent types of AEs, the

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number and percentage of patients who reported the AE was determined. Summaries included classifications by intensity (mild, moderate, severe, or life-threatening) and relationship to treatment (certain, probable, possible, doubtful, no relation, or can't determine). The SAEs and AEs that were considered by the investigator to be possibly related to treatment were also identified.

5. RESULTS – STUDY PATIENTS AND CONDUCT

5.1 NUMBER OF INVESTIGATORS AND PATIENTS PER INVESTIGATOR

This study was conducted at a single site by one Principal Investigator shown below.

A total of 54 patients were screened, 50 enrolled, and 47 (94%) of 50 patients completed the study.

5.2 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Baseline characteristics are presented in Table 2 below. Fifty (50) patients were enrolled in this study; all had signs of facial lipoatrophy (sunken cheeks) at baseline. At baseline, the mean TCT was 3.0 ± 0.6 mm; mean adipose tissue thickness was 0.5 ± 0.7 mm, and the mean VAS scores was 6.6 ± 2.3 (arbitrary units). Note that patients had little or no adipose tissue in the genal area at baseline indicating severe facial lipoatrophy (median adipose thickness of 0 mm, ranging from 0.0 to 2.1 mm).

The patient population was predominantly Caucasian males; only one woman participated in the study. All (100%) patients had lipodystrophy exhibited by sunken cheeks, 86% patients had leg fat loss, 44% had arm fat loss, 30% exhibited waist enlargement, and 20% had breast enlargement. None of the patients had enlargement of the dorsocervical fat pad "buffalo hump".

Forty-nine (49) patients were examined and found to be normal in the cardiac, pulmonary and digestive systems. Forty-six (46) of 49 patients had normal findings on cutaneous examination and 44 of 50 patients had normal neurological findings.

Additional summary information on baseline demographics is provided in Table 1.1 (Section 10), and baseline patient characteristics are summarized in Table 1.2 (Section 10). Baseline physical examination findings are summarized in Table 1.3 (Section 10). Complete details of Baseline characteristics for each patient are provided in Listings 1 to 17 (Appendix C).

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Table 2: Baseline Demographic Characteristics, N (%)	
Demographic Characteristic	All Patients, N=50
Age (years) Mean ± SD range (min, max)	44.9 ± 6.8 33 - 58
Gender Male Female	49 (98%) 1 (2%)
Race Caucasian Hispanic North African Caribbean Black African	42 (84%) 3 (6%) 2 (4%) 2 (4%) 1 (2%)
Weight, Kg (N=47) mean ± SD	65.0 ± 7.4
Height, cm, (N=43) mean ± SD	175.7 ± 6.3
AIDS Patients	25 (50%)
HIV Viral Load (copies/ml) median (range)	200 (50-96,114)
HIV Viral Load (<5000 copies/ml) Patients	43 (86%)
CD4 T-Cells (mm³) Mean ± SD	397.1 ± 168
Lipodystrophy Sunken cheek Arm fat loss Leg fat loss Dorsocervical fat pad Breast enlargement Waist Enlargement	50 (100%) 22 (44%) 43 (86%) 0 10 (20%) 15 (30%)
TCT both cheeks (mm) mean ± SD median range (min , max)	3.0 ± 0.6 3.0 2.0 – 5.5
Adipose tissue thickness both cheeks (mm) mean ± SD median range (min, max)	0.5 ± 0.7 0 0.0 – 2.1
VAS for well-being mean ± SD (of median values) median	6.6± 2.3 6.4
Source Data: Table 1.1, 28OCT03 – V_FINAL, DEMOG.SAS Table 1.2, 28OCT03 – V_FINAL, DEMOG2.SAS	

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5.3 ACCOUNTABILITY AND POOLABILITY

5.3.1 Accountability

Fifty-four (54) patients were screened, 50 patients were eligible, enrolled, and treated in this study. Four screen failures did not meet the entry criteria and were not treated. Forty-seven (47, 94%) of fifty patients completed the study. One patient discontinued due to an SAE, and two other patients withdrew from the study of their own choice. Reasons for discontinuation from the study are provided in Section 5.6.

5.3.2 Data Poolability

Not applicable since this was a single center study.

5.4 PROTOCOL DEVIATIONS

A number of the assessments and treatment sessions though assigned to a particular study day or week, actually occurred at varying times relative to the first injection session. These variations from the pre-defined times were due to scheduling difficulties between the hospital, the radiology facility and treating dermatologist. Also, the protocol did not define any specific visit-window criteria. The most common type of deviation included variations in the timing of treatments (not always at 2 week intervals). Similarly, the actual period for ultrasound measurements might have varied due to scheduling issues. The retrospective review of records showed that the ultrasound measurements scheduled for Week 6/8 correspond more closely to a period of 10 weeks from the initial treatment.

The source record verification process or data listings revealed the following deviations:

- ██
  ██
- ██
- ███████████████████████████ ns.
- ██

5.5   ADMINISTRATION OF DEVICE

5.5.1 Treatment and duration

Overall, the number of injection sessions per patient ranged between 3 and 6, with most patients (86%) having 4 or 5 injection sessions (Table 3).

All 50 patients had at least 3 injection sessions. Injection sessions were scheduled for Days 0, 15, 30 45 and 60 (if needed). However, as noted above, the injection sessions were not always performed according to schedule due to patient and physician availability.

The number of injection sessions is also summarized in Table 1.5 (Section 10) and complete details of all injection sessions for each patient are provided in Listings 19 (see Appendix C).

Table 3: Number of Treatment Sessions in All Treated Patients	
Injections	Total (N=50) n (%)
3 Sets of Injections	4 (8.0)
4 Sets of Injections	24 (48.0)
5 Sets of Injections	19 (38.0)
6 Sets of Injections	3 (6.0)
Data Source: Table 1.5, 28OCT03 – V_FINAL, INJECT.SAS	

5.5.2 Compliance

All treatments were administered by a single, dermatologist ███████████████████████, ████ Therefore patients were deemed to be 100% compliant.

5.5.3 Product Accountability

The product is available in ████ as a marketed product licensed for use as a "wrinkle-filling agent". The treating dermatologist, ████████████ obtained commercially available product for the injection sessions. The treating dermatologist did not maintain product accountability records. However, there are individual patient treatment records maintained at the study site.

Although not specifically recorded for each individual patients, the lot numbers of product used in this study were ███████████████████████████. Copies of the Certificate of Analysis for all product are provided in Appendix A.3.3.

5.6 PATIENT DISPOSITION AND DISCONTINUATION

Summary of patient disposition are provided in Table 4, additional details can be found in Listing 22 (Appendix C).

Table 4: Summary of Patient Disposition: All Treated Patient Population, N (%)	
End of Study Status Discontinuation Reason	**Total** (N=50)
Completed	
Total	47 (94.0)
Discontinued	
Total	3 (6.0)
Adverse Event	1 (2.0)
Patient Choice	2 (4.0)
Data Source: Table 1.4, 28OCT03 – V_FINAL, DISPOS.SAS	

Fifty patients entered the study and 47 (94%) completed through Week 96. Patients ▇ and ▇ withdrew after Week 72 at their own request. Both of these patients are included in the list of patients who did not provide consent for verification of their data, so no further information including the patient CRFs is available in either case. Patient ▇ was diagnosed on 09/10/2002 with a severe, high-grade, large cell lymphoma. This patient received five injection sessions (last treatment session 05/16/01). Although the SAE was considered unrelated to the study treatment, the patient withdrew from the study prematurely. Accordingly, data for this patient are available for up to Week 48. A copy of the CRF for patient ▇ s included in Appendix D.

No deaths occurred during the study.

5.7 CONCOMITANT MEDICATIONS

Antiretroviral history is listed for each patient in Listings 4 and 9 (Appendix C). Current treatment with Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Protease Inhibitors (PIs) and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) is listed in Listings 6, 7, and 8 (Appendix C), respectively.

All patients continued their antiretroviral therapy throughout the study; ten patients missed a daily dose once, one patient missed two of their daily doses and 1 patient missed 5 doses. Additionally patient 25 was noted to have missed 50% of their antiretroviral treatment at the Week 96 visit. All other patients did not report any missed doses.

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One patient (Patient█received a prohibited medication, interferon, twice during the study for the treatment of Hepatitis C virus infection.

Details of anti-retroviral treatment during the study are provided in Listings 15 and 26 (Appendix C). Concomitant medications for conditions other than Antiretroviral treatment are given in Listings 25 (Appendix C).

6. SAFETY AND EFFECTIVENESS DATA

6.1 INDIVIDUAL SAFETY DATA

All safety data listings are included in Appendix C. These data include AE and SAE listings (Listings 23 and 24), changes in the results of clinical examinations (Listings 12 and 13) as well as laboratory evaluations (Listing 17). Data from blood lactic acid levels are provided in Listing 18.

6.2 INDIVIDUAL EFFECTIVENESS DATA

Data from ultrasound measurements are provided in Listing 20 (Appendix C), and the VAS scores from QoL evaluations in Listing 21 (Appendix C).

6.3 DEVICE FAILURES AND REPLACEMENTS

No problems with the device were reported.

6.4 PATIENT COMPLAINTS

No patient complaints were reported during the study, although the Investigator did not actively solicit and record this information.

7. RESULTS OF STATISTICAL ANALYSIS FOR CLINICAL INVESTIGATION

7.1 SAFETY

7.1.1 Adverse Events

7.1.1.1 Overview of Adverse Events

Forty-eight (96%) of all patients reported a total of 202 treatment-emergent AEs (TEAEs) as shown in Table 5. This table provides the most commonly reported AEs (by ≥ 5% of patients) during the study. A total of 15 patients reported 19 events coded as injection site hemorrhage (MedDRA preferred term); of these, 17 were recorded as hematoma, and 2 events were bleeding.

Summary information on TEAEs is provided in Tables 3.2, and 3.3 (Section 10).

Table 5: Summary of Most Common Treatment-Emergent Adverse Events Reported by (≥ 5%) Patients			
		Incidence[a]	
System Organ Class MedDRA Term	n	Number (%) of Patients	Total No. of AEs
Total, all AEs	50	48 (96)	202
Gastrointestinal disorders			
Abdominal pain - nos	50	4 (8)	4
Diarrhoea - nos	50	6 (12)	6
General disorders and administration site conditions			
Injection site bruising	50	3 (6)	3
Injection site hemorrhage (hematoma)	50	15 (30)	19
Injection site nodule[b]	50	26[b] (52)	27
Infections and infestations			
Influenza like illness	50	3 (6)	3
Nasopharyngitis	50	3 (6)	3
Investigations			
Blood triglycerides increased	50	8 (16)	10
Gamma-glutamyltransferase increased	50	3 (6)	3
Transaminases increased	50	4 (8)	4

a: At each line, a patient may be classified in more than one category or more than once in the same category.
b: ▮▮▮▮▮▮▮▮had two events of mild and moderate intensity each.
Abbreviation: nos = not otherwise specified
Data Source: Table 3.6, 28OCT03 – V_FINAL, AETABLE4.SAS

7.1.1.2 Intensity of Adverse Events

A majority of the TEAEs (159 of a total 202) reported in this study were mild or moderate in intensity (Table 3.6, Section 10). Seventeen (34%) patients reported 25 events of severe intensity. Increased triglycerides, considered to be of severe intensity, were most frequently reported (for 3 patients); all other events of severe intensity were reported only once in this study. One episode of treatment-related injection site hemorrhage (verbatim term hematoma on right and left cheeks) and one episode of edema was of severe intensity, and the remaining events were either mild or moderate. The aforementioned severe hematoma resolved in 18 days and the edema resolved in 3 days. A complete table with additional information is included in Table 3.2 (Section 10).

7.1.1.3 Relationship of Adverse Events to Treatment

A total of 35 (70%) patients reported one or more treatment-related AEs (Table 6); the most common being injection sites nodules and hemorrhage (hematoma and/or bleeding).

Nodules (27 individual events) were noted in 26 of the 50 treated patients. The onset of nodules from first injection of product occurred anywhere from 9 days until over 2 years (748 days). The majority of nodules appeared within the first year (20, 74%). Five (19%) of the nodules resolved over the course of the study. The remaining nodules were ongoing at the time of last follow-up. The majority of these nodules were noted to be of mild intensity (21, 78%), 4 were considered moderate and 2 were of unknown intensity (See Listing 23.1, Appendix C).

One episode each of treatment-related injection site hemorrhage and another one of edema was severe; all others were of mild or moderate intensity. Both of the severe intensity events resolved spontaneously, hemorrhage in 18 days and edema in 3 days. The verbatim terms were "hematoma on right and left cheeks" (Patient 19), and "immediate reaction edema with mandibular drop" (Patient 18). Additional details on the intensity of treatment-emergent AEs are presented in Table 3.2 and 3.6 (Section 10).

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Table 6: Treatment Emergent Adverse Events at Least Possibly Related to Treatment		
System Organ Class MedDRA Term	n	Total Incidence n (%)
Overall		
Patients with at least Possibly Related AE's	50	35 (70.0)
General disorders and administration site conditions		
Injection site bruising	50	3 (6.0)
Injection site hemorrhage	50	15 (30.0)
Injection site nodule	50	26 (52.0)
Injection site edema	50	2 (4.0)

ᵃAt each line, a patient was classified only one time as the most probable category.
Note: Data from patients ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮e not source-verified.
Source Data: Table 3.4, 28OCT03 – V_FINAL, AETABLE2.SAS

7.1.2 Unanticipated Adverse Device Effects (UADES)

No Unanticipated Adverse Device Effects were reported for any patient during the trial.

7.1.3 Serious Adverse Events

Table 7 shows that a total of 6 (12%) patients each experienced one serious adverse event (SAE). None of the SAEs were considered to be related to the device by the investigator. Individual patients narratives are provided in Section 11. Additional information for the SAEs is provided in Listing 24 (Appendix C).

Table 7: Incidence of Serious Adverse Events in All Patients		
System Organ Class MedDRA Term	Patient No.	SAE[a], n (%)
Total No. of Patients with SAE		6 (12.0)
Blood and lymphatic system disorders		
Anemia folate deficiency	19	1 (2.0)
Investigations		
Bacterial sepsis	3	1 (2.0)
Musculoskeletal and connective tissue disorders		
Dupuytren's contracture	10	1 (2.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Lymphoma nos	53	1 (2.0)
Skin and subcutaneous tissue disorders		
Skin ulcer	21	1 (2.0)
Surgical and medical procedures		
Arteriovenous fistula operation	11	1 (2.0)

a: No serious adverse events (SAEs) were considered to be related to the device by the investigator.
Source Data: Table 3.5, 30OCT03 – V_FINAL, AETABLE3.SAS.

7.1.4 Clinical Laboratory Assessments

7.1.4.1 CD4 T-Cell Count

There were no clinically significant changes from baseline in CD4 T-cells, although there was a statistically significant change from baseline at Week 72 (Table 8).

Table 8: Change From Baseline in CD4 T-Cells				
		CD4 T-Cells (mm^3)		
Visit	n	Change from Baseline Mean (SD)	(Min , Max)	Within-Group p-value
Week 6	12	75.1 (126.8)	(-51.0 , 345.0)	0.065
Week 12	26	-15.0 (95.8)	(-283.0 , 132.0)	0.432
Week 16	5	118.4 (168.0)	(-119.0 , 288.0)	0.190
Week 24	46	-3.6 (111.7)	(-286.0 , 365.0)	0.830
Week 48	45	27.8 (135.9)	(-326.0 , 389.0)	0.178
Week 72	48	55.8 (136.9)	(-292.0 , 353.0)	0.007
Week 96	46	30.2 (148.4)	(-201.0 , 442.0)	0.175

Data Source: Table 3.1, 28OCT03 – V_FINAL, CHGLABS.SAS

7.1.4.2 Viral Load

There were no clinically significant changes from baseline in viral load, although there was a statistically significant change from baseline at Weeks 72 and 96 (Table 9).

Table 9: Change From Baseline in Viral Load				
		Viral Load ($\log_{10}$ copies /mL)		
Visit	n	Change from Baseline Mean (SD)	(Min , Max)	Within-Group p-value
Week 6	12	-0.4 (0.8)	(-2.3 , 0.3)	0.114
Week 12	25	-0.0 (0.5)	(-1.7 , 0.9)	0.850
Week 16	4	-0.7 (1.2)	(-2.3 , 0.4)	0.321
Week 24	44	-0.1 (0.6)	(-2.2 , 1.5)	0.183
Week 48	45	-0.2 (1.0)	(-2.5 , 2.8)	0.171
Week 72	46	-0.3 (0.6)	(-1.8 , 0.9)	<0.001
Week 96	44	-0.3 (0.7)	(-2.3 , 1.3)	0.007

Data Source: Table 3.1, 28OCT03 – V_FINAL, CHGLABS.SAS

7.1.4.3 Lactic Acid Levels

There were no clinically or statistically significant changes from baseline in blood lactic acid during the study (Table 10).

Table 10: Change From Baseline in Blood Lactic Acid				
	Blood lactic acid (mmol/L)			
Visit	n	Change from Baseline Mean (SD)	(Min , Max)	Within-Group p-value
Week 6	1	-1.9	(-1.9 , -1.9)	> 0.999
Week 12	1	0.2	(0.2 , 0.2)	> 0.999
Week 16	0	N/A	N/A	> 0.999
Week 24	11	0.2 (0.9)	(-1.2 , 1.5)	0.472
Week 48	14	0.1 (0.7)	(-1.5 , 1.2)	0.783
Week 72	16	0.0 (0.9)	(-2.3 , 1.1)	0.957
Week 96	16	0.4 (0.9)	(-0.8 , 2.9)	0.057

Abbreviation: N/A = not available.
Data Source: Table 3.1, 28OCT03 – V_FINAL, CHGLABS.SAS

All data for the continuous laboratory parameters shown here can be found with additional details in Table 3.1 (Section 10).

7.1.5 Safety Summary

Forty-eight (96%) of 50 treated patients reported a total of 202 treatment-emergent adverse events (AEs). The most frequently reported AEs were injection site nodule (26, 52%), increased triglycerides (8, 16%), injection site hemorrhage (15, 30%), and diarrhea (6, 12%). Each episode of injection site bruising (3), hemorrhage (15, includes the events hematoma and bleeding), nodules (26, 52%) and edema (2, 4%) was considered by the investigator to be either certainly, probably or possibly related to the New-Fill treatment.

Most of the treatment-emergent adverse events were mild or moderate in intensity. Seventeen (34%) patients reported 25 events of severe intensity. Increased triglycerides, considered to be of severe intensity, were most frequently reported (for 3 patients); all other events of severe intensity were reported only once in this study. One episode of treatment-related injection site hemorrhage (verbatim term hematoma on right and left cheeks) and one episode of edema was of severe intensity, and the remaining events were either mild or moderate. The aforementioned severe hematoma resolved in 18 days and the edema resolved in 3 days.

A total of 6 (12%) patients experienced one serious adverse event (SAE). None of the SAEs were considered to be related to treatment with PLLA. No deaths were reported in this study.

There were no clinically significant changes from baseline in the CD4 T-cell counts, viral load or blood lactic acid, although a few statistically significant changes were identified at isolated time points. These findings were most likely due to the patients' underlying disease.

7.2 EFFECTIVENESS

Table 11 presents mean changes from baseline in genal TCT measurements throughout the study (parametric analysis), and these data are depicted in Figure 2 below. The findings of the non-parametric analysis (Table 2.2.1, Section 10) supported the findings of the parametric analysis (Table 11). Additional details for the responder rate summary results can be found in Table 2.1 (Section 10).

Mean increases above the baseline (3.0 ± 0.6; see Table 11 below) ranged from 5.2 mm to 7.2 mm throughout the study period, and these increases from baseline were statistically significant ($p < 0.001$) at each time point. It should be noted that every patient treated with the device responded positively (although not to the pre-defined responder criteria of 10 mm), since measurements of total cutaneous thickness showed a minimum post-treatment increase above baseline of at least 2.2 mm (at Week 8).

The number of "responders" (with gross TCT $\geq$ 10 mm) peaked (61%) at Week 48 (Month 12). Therefore, the null hypothesis was not rejected for this parameter since the responder rate at Month 6 was only 38%. Although the number of responders reached the 60% criteria in the study only once (using the arbitrarily set criteria of 10 mm), it should be noted that if the *a priori* responder criteria was set to 8 mm, all of the patients in the study would have been considered as a responder at one point or another during the study (refer to individual response profiles in Section 10). Statistically significant changes from baseline in TCT were observed at every time point throughout the study, and the null effectiveness hypothesis for this parameter was rejected.

Table 11: Change from Baseline in Total Cutaneous Thickness (mm) by Visit, Parametric Analysis: All Patients

Visit	n	Baseline Mean (SD)	Treatment Mean (SD)	Change From Baseline			
				Mean (SD)	(Min , Max)	p-value[a]	Responder, n (%)
Day 60 (Week 8)[b]	48	3.0 (0.6)	8.2 (1.7)	5.2 (1.7)	(2.2 , 8.7)	<0.001	9 (18.8)
Week 24 (Month 6)	50	3.0 (0.6)	9.4 (1.5)	6.4 (1.6)	(3.0 , 9.1)	<0.001	19 (38.0)
Week 48 (Month 12)	49	3.0 (0.6)	10.2 (1.2)	7.2 (1.3)	(4.3 , 9.6)	<0.001	30 (61.2)
Week 72 (Month 18)	48	3.0 (0.6)	10.2 (1.2)	7.2 (1.3)	(3.5 , 9.3)	<0.001	24 (50.0)
Week 96 (Month 24)	45	3.0 (0.6)	10.0 (1.3)	7.0 (1.4)	(3.9 , 10.2)	<0.001	19 (42.2)

[a]The p-value is based on the paired t-test.
[b]Per Protocol Amendment 1, the Day 45 (Week 6) visit was changed to the Day 60 (Week 8) visit.
Note: Data from patients ▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇ re not source-verified.
Data Source: Table 2.2.2, 28OCT03 - V_FINAL, PARA_CHGTCT.SAS
  Table 2.1, 28OCT03 – V_FINAL, RESPOND.SAS

Although the analysis grouped ultrasound measurements into visits, it is also important to view the individual responses over time since there was variability in the timing of ultrasounds and injections. Combined individual total cutaneous thickness responses over time are depicted in Figure 3 (denoted as circles). Note that the majority of treatment sessions occurred within the first 20 weeks of the study (denoted as stars in the figure), and all of the patients markedly improved from baseline. In addition, individual patient responses to treatment over time are presented in Section 10 for the 50 individual patients.

Date - 14 November 2003
Document Status - FINAL

Figure 2: Evolution of the Total Cutaneous Thickness as Measured by Ultrasonography: All Patients
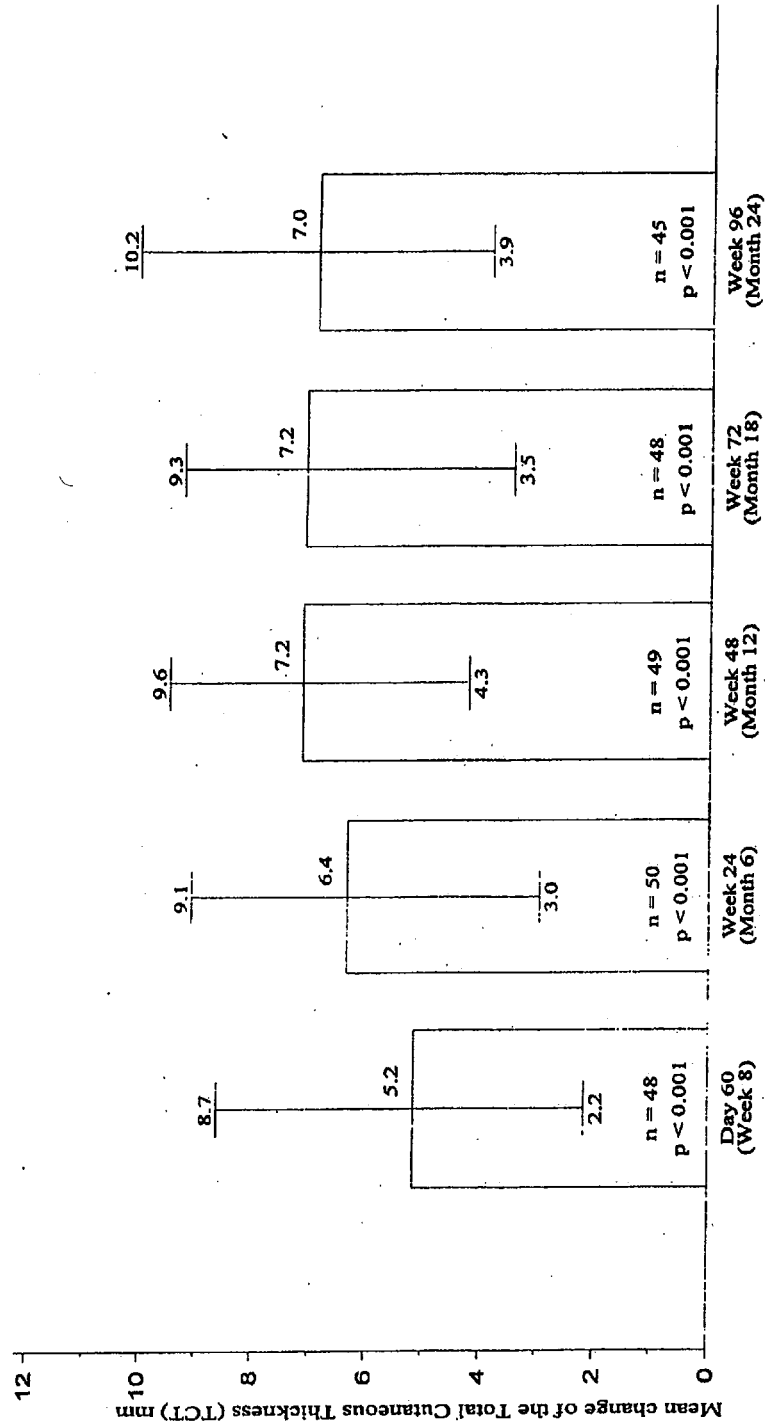
Extreme values: Max-Min; The p-value is based on the paired t-test.
Per Protocol Amendment 1, the Day 45 (Week 6) visit was changed to the Day 60 (Week 8) visit.

Data Source: Figure 1.1, 04NOV03, tct_bar_graph.sas

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Figure 3: Profile of Dermal Thickness by Ultrasound by Weeks From First Injection
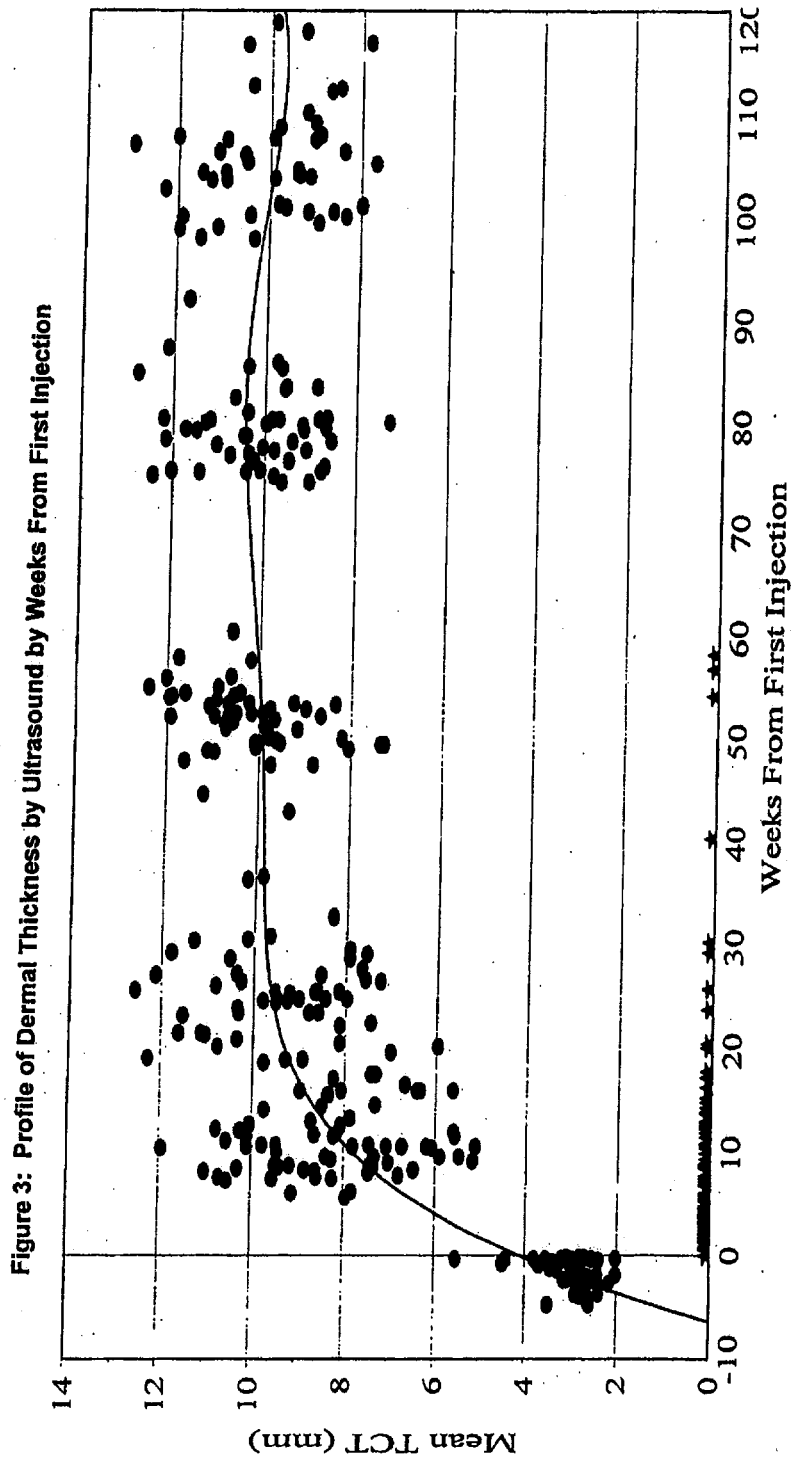
★   Denotes treatment sessions with PLLA

Source Data: Figure Combined Profile, 03NOV03, comb_profiles.sas

7.2.1 Acute Procedural Success

As shown in the figures above, all patients showed consistent increases in TCT over baseline within the first two to three months following initial device implantation. The results from non-parametric analysis were similar, and are provided in Section 10. Six months (Week 24) after the initial injection session, 19 patients (38%) were classified as "responders", i.e. gross TCT ≥ 10 mm (Table 11). The mean TCT values increased from a baseline of 3.0 ± 0.6 mm to 9.4 ± 1.5 mm at Week 24 (a three-fold increase). These increases in TCT were statistically significant (p<0.001).

7.2.2 Long-term Clinical Success

The effectiveness of the device observed in the short-term (first 6 months) is consistent with the significant increases in TCT maintained over the two-year follow-up period (refer to data presented in Figure 2, Figure 3, and Table 11).

7.2.3 Results from Subpopulation

Results from a subpopulation of ▌ of the 50 enrolled patients, whose source records were verified, are presented in Table 12. In this analysis, data from ▌▌▌ are excluded to determine if the patients who were not verified had a significant impact on the overall outcome (see Tables 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, and 4.8 included in Section 10). It was determined that excluding these data had no effect on the overall conclusions drawn from the analyses when verified and unverified data are included. Table 12 provides the parametric analyses from change in TCT from baseline over time for the source verified population.

Table 12: Change from Baseline in Total Cutaneous Thickness (mm) by Visit, Parametric Analysis: Source-Verified Population

Visit		Baseline Mean (SD)	Treatment Mean (SD)	Change From Baseline			
				Mean (SD)	(Min, Max)	p-value[a]	Responder, n (%)
Day 60 (Week 8)[b]						<0.001	
Week 24 (Month 6)						<0.001	
Week 48 (Month 12)						<0.001	
Week 72 (Month 18)						<0.001	
Week 96 (Month 24)						<0.001	

a: The p-value is based on the paired t-test.
b: Per Protocol Amendment 1, the Day 45 (Week 6) visit was changed to the Day 60 (Week 8) visit.
Note: ▌▌▌
Data Source: Table 4.4, 04NOV03 - V_FINAL, SUB_PARAMET_CHGTCT.SAS;
Table 4.3, 03NOV03 – V_FINAL, RESPONDSUB.SAS

7.2.4 Quality of Life

Median change in QoL scores are provided in Table 13.

Table 13: Change from Baseline in Quality of Life by Visit, Non-Parametric Analysis: All Patients						
				Change From Baseline		
Visit	n	Baseline Median (SD)	Treatment Median (SD)	Median (SD)	(Min , Max)	p-value[a]
Week 12 (Month 3)	20	6.3 (2.6)	8.0 (2.3)	0.3 (2.7)	(-2.9 , 10.0)	0.185
Week 24 (Month 6)	32	6.3 (2.5)	7.9 (1.8)	0.8 (2.4)	(-3.9 , 10.0)	0.012
Week 48 (Month 12)	37	6.6 (2.2)	8.0 (1.7)	0.8 (2.3)	(-2.9 , 10.0)	0.019
Week 72 (Month 18)	38	6.7 (2.4)	7.8 (1.8)	0.4 (2.5)	(-3.3 , 10.0)	0.213
Week 96 (Month 24)	38	6.1 (2.3)	7.5 (1.8)	0.4 (2.7)	(-3.9 , 10.0)	0.150

a: The p-value is based on the Wilcoxon Signed-Rank test.
Note: Quality of Life is measured on a scale of 0-10 where 0-4: Unsatisfactory physical and/or emotional state, 5: OK, 6-10: Satisfactory physical and/or emotional state.
Data from patients███████████████████████are not source-verified, but included here.
Data Source: Table 2.3.1, 28OCT03 - V_FINAL, CHGQOL.SAS

The Visual Analogue Scale (VAS) for evaluating "Global Well-Being" assessed the quality of life. This was measured on a scale of 0-10, where 0-4: Unsatisfactory physical and/or emotional state, 5: OK, and 6-10: Satisfactory physical and/or emotional state. Baseline median VAS scores for QoL ranged between 6.1 and 6.7, which relate to the characteristic description of "satisfactory physical and/or emotional state". After treatment, the increase in the median VAS scores ranged between 0.3 and 0.8 over a period of 96 weeks. Statistically significant improvements in QoL were observed at Months 6 and 12. However, it should be noted that the scale used for this study was arbitrary and not validated.

The mean increases from baseline in VAS scores as determined by parametric analysis were similar, with statistically significant (p<0.05) improvements at Weeks 24 and 48. The parametric analysis is provided in Table 2.3.2, Section 10.

Table 14 provides the non-parametric analysis of change from baseline in QoL of a subpopulation of ██ of 50 patients (whose source records were verified) over time.

Table 14: Change from Baseline in Quality of Life by Visit, Non-Parametric Analysis: Source-Verified Population

Visit		Baseline Median (SD)	Treatment Median (SD)	Change From Baseline		
				Median (SD)	(Min , Max)	p-value[a]
Week 12 (Month 3)						0.070
Week 24 (Month 6)						0.007
Week 48 (Month 12)						0.029
Week 72 (Month 18)						0.084
Week 96 (Month 24)						0.105

[a]The p-value is based on the Wilcoxon Signed-Rank test.
Note: Quality of Life is measured on a scale of 0-10 where 0-4: Unsatisfactory physical and/or emotional state, 5: OK, 6-10: Satisfactory physical and/or emotional state.

Data Source: Table 4.5, 03NOV03 - V_FINAL SUBQOL.SAS

7.2.5 Photographic results

Photographs taken at baseline confirm that patients had severe lipoatrophy. Inspection of the post-treatment photographs confirms marked improvements in facial appearance following treatment-related increases in the volume of the lipoatrophic genal area. Due to restrictions in the photographic release and confidentiality issues, photographic data are not included in this report. However, photographs are available at the investigative site for those patients who specifically consented to allow the use of their photographs in a regulatory submission to the US FDA.

7.2.6 Effectiveness Summary

Objective ultrasound data demonstrate that an individualized treatment course of New-Fill is effective in the correction of facial lipoatrophy with statistically significant (p<0.001) increases in dermal thickness. These significant changes from baseline were observed at Week 8; showed progressive improvement until Week 48; and were sustained through Weeks 72 and 96. In addition, dermal thickness increases were corroborated with visible improvements in the patient's outward appearance.

8. DISCUSSION AND OVERALL CONCLUSIONS

8.1 DISCUSSION

Lipoatrophy is a severe morphologic syndrome with psychological consequences for most affected patients. The use of a placebo or untreated control group is not acceptable; therefore, the study was performed as an open-label, non-comparative study with quantitative measurements of facial thickness and long-term follow-up.

The results of this open-label, non-comparative pilot study showed that the use of facial implants with PLLA (New-Fill®) could produce significant improvement in the restoration of facial fat thickness and appearance in treatment-experienced HIV-infected patients with severe facial fat loss. The data demonstrate clearly the correction of facial lipoatrophy with a significant increase in dermal thickness at Week 8, which progressively improved until Week 48 (3-fold increase from baseline) and was sustained to Week 96, end-of-the-study. These results are considered to be clinically relevant. Overall improvement was clearly observed, accompanied by a significant increase in patient QoL scores between Baseline and Week 48.

The progressive increase of dermal thickness surrounding the PLLA injection site (up to Week 48) is consistent with the mechanism of action of such bioactive resorbable material

Treatment and remediation of severe lipoatrophy seen in the HIV-positive patient population should prove to be of remarkable value to those who may have endured potential psychological and social consequences due to an obvious and inescapable deformity. A reasonable treatment course with a safe and effective device that helps reduce or eliminate the negative consequences and experiences by the HIV-positive population should provide a significant value to overcome the impediments due to a complex disease.

Despite biodegradable materials being widely available for use in corrective and cosmetic procedures, there are no substantial data based on quantitative measurements available in the literature to evaluate similar intervention in the treatment of HIV-associated lipoatrophy. Two previous, small pilot studies with 24 weeks of follow-up have suggested the efficacy of PLLA to improve facial lipoatrophy.[27,28] Other therapeutic approaches to correct fat loss in HIV-associated lipoatrophy have also been reported in different studies.[29,30] The use of hyaluronic acid injection has been associated with a rapid decline in the degree of correction and loss of esthetic improvement following administration.[29] Studies of autologous fat transplantation injections to correct deep subcutaneous tissue losses have shown absorption of the transplanted fat with a graft survival rate of 40% to 60% at one year after treatment.[30] The durability of autologous fat transplantation depends on several factors, including the harvesting and grafting technique, quality of transplanted tissue, and vascularity of the recipient site,[30,31] and the results appear to be highly dependent on the surgeon's level of training. In addition,

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this approach requires the use of general anesthesia and prolonged hospitalization. In contrast, the findings of this study suggest that PLLA implants have little impact on the daily activities of treated patients since the procedure can be performed on an outpatient basis without any need for recovery time. Furthermore, the simplicity of the procedure should lead to the rapid training of health care practitioners.

Despite the total injected quantity of PLLA in this study being higher than that used in the treatment of wrinkles and scars, no serious, treatment-related AEs were observed during the study. The most frequent adverse event was palpable, non-visible subcutaneous nodules. Approximately half of the patients reported nodules during the study. Most nodules occurred during the first year of the study period. Of all reported nodules, five resolved spontaneously. The majority of the nodules were of mild intensity, and not bothersome to the patients.

In the absence of a pathogenetic treatment (i.e. treating the underlying cause) and since other treatment approaches, such as modification of the patient's antiretroviral regimen or use of insulin-sensitizing agents or growth hormone have failed to show clinically significant changes in facial lipoatrophy,[32-36] the use of biodegradable materials to improve physical appearance offers a significant progress in therapeutic management of HIV-related lipoatrophy.

8.2   OVERALL CONCLUSIONS

- Facial implants with PLLA (New-Fill®) significantly improve the signs of facial lipoatrophy as demonstrated by increases from baseline in dermal thickness by the Week 8 visit. ·

- Significant improvements in dermal thickness were sustained throughout the two-year study. These were accompanied by significant increases in patient QoL scores (over well-being) between baseline and Weeks 24, and 48.

- An individualized treatment course of 3 to 6 injection sessions of New-Fill® offers a safe and effective treatment for the signs of facial lipoatrophy that may help alleviate the psychological and social consequences of facial lipoatrophy.

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9. REFERENCES

1. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N. Engl.J. Med.* 1998, 338: 853-860.

2. Carr A, Samaras K, Burton S, Freund 1, Chisholm J, Cooper DA. A syndrome of peripheral lipodystrophy, hyperlipidemia and insulin resistance due to HIV protease inhibitors. *AIDS* 1998, 12: F51-F58.

3. Lo JC, Mulligan K, Tai VW, Algren H, Schambelan M. Buffalo hump in men with HIV-1 infection. *Lancet* 1998, 351: 867-870.

4. Carr A, Samaras K, Chisholm J, Cooper DA. Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. *Lancet* 1998, 351: 1881-3.

5. Saint-Marc T, Touraine IL. Buffalo hump in HIV-1 infection. *Lancet* 1998 352: 319-320.

6. Madge S, Kinloch-DeLoes S, Tyrer M, Johnson MA. Lipodystrophy in patients naïve to protease inhibitors. *AIDS* 1999, 13: 735-737.

7. Gervasoni C, Ridolfo AL, Trifiro G, et al. Redistribution of body fat in HIV-infected women undergoing combined antiretroviral therapy. *AIDS* 1999, 13: 465-471.

8. Behrens GMN, Dejam A, Schmidt H, et al. Impaired glucose tolerance, beta cell function and lipid metabolism in HIV patients under treatment with protease inhibitors. *AIDS* 1999,13: F63-F70.

9. Visnegarwara F, Krause KL, Musher DM. Severe diabetes associated with protease inhibitor therapy. *Ann Intern Med* 1997, 127: 947.

10. Saves M, Raffi F, Capeau J, Lang JM, Peyramond D, Basdevant A, Roloff S, Chêne G, Rozenbaum W, and the APROCO study Group. Factors related to the presence of fat redistribution in HIV-infected patients treated with protease inhibitor containing regimens – APROCO cohort. 7th Conference on Retrovirus and Opportunistic Infections – San Francisco – January 30 – February 2, 2000 (Abstract 14).

11. Boufassa F, Dulioust A, Lascaux A.S, Bodart L, Goujard C and the Liposud Study Group. Lipodystrophy and metabolic disorders in 646 HIV-1 infected patient previously treatment with or without a protease inhibitor. 7th Conference on Retrovirus and Opportunistic Infections – San Francisco – January 30 – February 2, 2000. (Abstract 17)

12. Miller J.E, Emery S, French M, Baker D, Copper D.A, and the Australian Lipodystrophy Syndrome Res. Group. The Australian prevalence survey of lipodystrophy syndrome. 7th Conference on Retrovirus and Opportunistic Infections – San Francisco – January 30 – February 2, 2000. (Abstract 201)

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13. Raghavan S, Aidary A.H, Lester K, Santos S, Wang J, Medard F, El Sadr W. Gender differences in prevalence of body habitus changes and metabolic complications in HIV+ African, American and Latino individuals from Harlem. 7th Conference on Retrovirus and Opportunistic Infections – San Francisco – January 30 – February 2, 2000. (Abstract 27)

14. Muurahainen N, Santos G, Kleintop M, Pettit R, Balser J, Falutz J, Glesby M, Kotler D, and the Salsa Investigator Group. Gender differences in HIV-associated adipose redistribution syndrome and update. 7th Conference on Retrovirus and Opportunistic Infections – San Francisco – January 30 – February 2, 2000. (Abstract 14)

15. Faure M. Complications des implants de silicone et autres matériaux dits inertes. [Complications from silicone implants and other so-called inert materials] Ann. Dermatol. Venerol. 1995; 122: 455-459.

16. Stegman SJ, Chu S, Bensch K, Armstrong R. A light and electron microscopic evaluation of Zyderm collagen and Zyplast implants in aging human facial skin. A pilot study. Arch. Dermatol 1987; 123: 1644 – 1649

17. Pons-Guiraud A. Réactions d'hypersensibilité retardée aux implants de collagène bovin. Etude sur 810 patients. [Delayed hypersensitivity reactions with bovine collagen implants. Study of 810 patients] Nouv. Dermatol. 1992; 11: 422-432.

18. Ghersetich I, Teofoli P, Benci M, Lotti T. Ultrastructural study of hyaluronic acid before and after the use of pulsed electromagnetic field, electrorydesis, in the treatment of wrinkles. Int. J. Dermatol. 1984; 33: 661-663.

19. Velly-Mores. Les premiers essais de comblement des rides par l'acide hyaluronique. [First trials for filling in wrinkles with hyaluronic acid] Nouv. Dermatol 1997; 16: 186-189.

20. Rokkanen P, Bôstman O, Vainionpa S, Makela E.A, Hirvensalo E, Partio E.K, Vihtonen K, Patiàla H, Tôrmàla P. Absorbable devices in the fixation of fractures. J. Trauma 1996; 40 (suppl): 5123-5127.

21. Simion M, Misitano U, Gionso L, Salvato A. Treatment of dehiscences and fenestrations around dental implants using resorbable and nonresorbable membranes associated with bone autografts: a comparative clinical study. Tnt. J. Oral Maxilofac. Implants. 1997; 12: 159-167.

22. Chadrashekar G, Udupa N. Biodegradable injectable implant systems for long term drug delivery using poly (lactic-co-glycolic) acid copolymers. J. Pharm. Pharmaco 1996; 48: 669-674.

23. Kaetsu I, Yoshida M, Asano M, Yamanaka H, L Mai K, Yuasa H et coll. Biodegradable implant composites for local therapy. J. Controlled Release 1987; 6: 249-263.

24. Gogolewski S, Jovanovic M, Perren SM, Dillon JG, Hughes MK. Tissue response and in vivo degradation of selected polyhydroxyacids: polylactides (PLA), poly(3-hydroxybutyrate) (PHB), and poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHB/VA). J Biomed Mater Res 1993; 27: 1135-1148.

25. Brady JM, Cutright DE, Miller RA, Barristone GC. Resorption rate, route, route of elimination, and ultrastructure of the implant site of polylactic acid in the abdominal wall of the rat. *J Biomed Mater Res* 1973; 7(2): 155-166.

26. Pietrzak WS, Sarver DR, Verstynen ML. Bioabsorbable polymer science for the practicing surgeon. *J Craniofac Surg* 1997; 8: 87-91.

27. Lafaurie M, Dolivo J, Boulu D, Madelaine I, Molina JM. Treatment of HIV-associated lipoatrophy of the face with intradermal injections of polylactic acid. Program and abstracts of the 9th Conference on Retrovirus and Opportunistic Infection. Seattle, February 24-28, 2002, Abstract 704-T.

28. Moyle G, Lysakova L, Brown S, Barton S. Polylactate (NewFill) injections subjectively and objectively improve appearance and reduce anxiety and depression scores in HIV positive persons with facial lipoatrophy: a randomized, open-label, immediate vs delayed therapy study. 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy. San Diego, September 27-30, 2002. Abstract H1934.

29. Olenius M. The first clinical study using a new biodegradable implant for the treatment of lips, wrinkles, and folds. *Aesthetic Plast Surg* 1998; 22: 97-101.

30. Pinski KS, Roenigk HH. Autologous fat transplantation: long term follow up. *J Dermatol Surg Oncol* 1992; 18: 179-184.

31. Kaminer SM, Omura NE. Autologous fat transplantation. *Arch Dermatol* 2001; 137: 812-814.

32. Carr A, Hudson J, Chuah J, Mallal S, Law M, Hoy J, Doong N, French M, Smith D, Cooper DA. HIV protease inhibitor substitution in patients with lipodystrophy: a randomized, controlled, open-label, multicentre study. *AIDS* 2001; 15: 1811-1822.

33. Carr A, Workman C, Smith DE, Hoy J, Hudson J, Doong N, Martin A, Amin J, Freund J, Law M, Cooper DA. Abacavir substitution for nucleoside analogs in patients with HIV lipoatrophy: a randomized trial. *JAMA* 2002; 288: 207-215.

34. Hadigan C, Corcoran C, Basgoz N, Davis B, Sax P, Grinspoon S. Metformin in the treatment of HIV lipodystrophy syndrome: a randomized controlled trial. *JAMA* 2000; 284: 472-477.

35. Sutinen J, Hakkinen AM, Westerbacka J et al. Rosiglitazone in the treatment of HAART associated lipodystrophy (HAL): a randomized, double-blind, placebo-controlled study. Program and abstracts of the 9th Conference on Retroviruses and Opportunistic Infections; February 24-28, 2002; Seattle, Washington. Abstract LB13.

36. Torres RA, Unger KW, Cadman JA, Kassous JY. Recombinant human growth hormone improves truncal adiposity and 'buffalo humps' in HIV-positive patients on HAART. *AIDS* 1999; 13: 2479-2481.

10. END-OF-TEXT TABLES AND FIGURES

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28OCT03

Polylactic Acid Implants (New-Fill): VEGA Study
Table 1.1
Baseline Demographics
All-Treated Population

Parameter	Total (N=50)
Gender [n (%)]	
Male	49 (98.0)
Female	1 (2.0)
Race [n (%)]	
Caucasian	42 (84.0)
Hispanic	3 (6.0)
North-African	2 (4.0)
Carib	2 (4.0)
Black African	1 (2.0)
Age (years)	
N	50
Mean (SD)	44.9 (6.8)
Median	45.5
Min, Max	33.0, 58.0
Weight (kg)	
N	47
Mean (SD)	65.0 (7.4)
Median	65.0
Min, Max	49.0, 78.0
Height (cm)	
N	43
Mean (SD)	175.7 (6.3)
Median	176.0
Min, Max	156.0, 188.0

Note: ████████████████████████████████

28OCT03 - V_FINAL   DEMOG.SAS

7-056

Polylactic Acid Implants (New-Fill): VEGA Study
Table 1.2
Baseline Patient Characteristics
All-Treated Population

Parameter	Total (N=50)
AIDS [n (%)]	
Yes	25 (50.0)
No	25 (50.0)
Viral Load [copies/ml]	
N	50
Median	200.0
Min, Max	50.0, 96114
Viral Load < 5000 copies/ml [n (%)]	
Yes	43 (86.0)
No	7 (14.0)
CD4 T-cells [mm^3]	
N	50
Mean (SD)	397.1 (168)
Median	391.5
Min, Max	127.0, 807.0
Sunken Cheek [n (%)]	
Yes	50 (100)
No	0 (0.0)
Arm Fat Loss [n (%)]	
Yes	22 (44.0)
No	28 (56.0)
Leg Fat Loss [n (%)]	
Yes	43 (86.0)
No	7 (14.0)
Dorsocervical Fat Pad [n (%)]	
Yes	0 (0.0)
No	50 (100)

[a]Scale of 0-10 where 0-4: Unsatisfactory physical and/or emotional state, 5: OK,
6-10: Satisfactory physical and/or emotional state.

Note: ▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬

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Polylactic Acid Implants (New-Fill): VEGA Study
Table 1.2
Baseline Patient Characteristics
All-Treated Population

Parameter	Total (N=50)
Breast Enlargement [n (%)]	
Yes	10 (20.0)
No	40 (80.0)
Waist Enlargement [n (%)]	
Yes	15 (30.0)
No	35 (70.0)
Adipose Tissue Thickness on both Cheeks, mm [mean of both sides]	
N	50
Mean (SD)	0.5 (0.7)
Median	0.0
Min, Max	0.0, 2.1
Total Cutaneous Tissue (TCT) Thickness on both Cheeks, mm [mean of both sides]	
N	50
Mean (SD)	3.0 (0.6)
Median	3.0
Min, Max	2.0, 5.5
Visual Analogic Scale for Well-Being[a]	
N	44
Mean (SD)	6.6 (2.3)
Median	6.4
Min, Max	0.0, 10.0

[a]Scale of 0-10 where 0-4: Unsatisfactory physical and/or emotional state, 5: OK,
6-10: Satisfactory physical and/or emotional state.
Note: ████████████████████████████████

28OCT03 – V_FINAL   DEMOG2.SAS

Polylactic Acid Implants (New-Fill): VEGA Study
Table 1.3
Baseline Physical Examination
All-Treated Population

Parameter	Total
Cardiac Exam [n (%)]	
Normal	49 (100)
Abnormal	0 (0.0)
Pulmonary Exam [n (%)]	
Normal	49 (100)
Abnormal	0 (0.0)
Digestive Exam [n (%)]	
Normal	49 (100)
Abnormal	0 (0.0)
Neurological Exam [n (%)]	
Normal	44 (88.0)
Abnormal	6 (12.0)
Cutaneous Exam [n (%)]	
Normal	46 (93.9)
Abnormal	3 (6.1)
Other Exam [n (%)]	
Normal	43 (89.6)
Abnormal	5 (10.4)
Note: ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮	
28OCT03 - V_FINAL	PE.SAS

Polylactic Acid Implants (New-Fill): VEGA Study
Table 1.4
Summary of Patient Disposition
All-Treated Population

End of Study Status Discontinuation Reason	Total (N=50)
Completed [n (%)]	
Total	47 (94.0)
Discontinued [n (%)]	
Total	3 (6.0)
Adverse Event	1 (2.0)
Patient Choice	2 (4.0)
Note: ▬▬▬▬▬▬▬▬▬▬	
28OCT03 – V_FINAL	DISPOS.SAS

11. PATIENT NARRATIVES

Serious adverse event (SAE) narratives are provided below for the six patients who were hospitalized during the study.

Bacterial sepsis (Patient): This ▮▮▮▮ld Caucasian male, with chronic infections of HIV and Hepatitis C virus, was hospitalized due to septicemia caused by Neisseria gonorrhea. This SAE occurred 1 year into the study (245 days after the New-Fill treatment session), and the patient recovered in 7 days and completed the study. This patient also reported six other AEs, 1 of mild intensity, 4 of moderate intensity and 1 severe AE of abdominal pain that resolved within 15 days of onset. All AEs and the SAE were considered by the investigator to be not related to the treatment device.

Dupuytren's contracture (Patient): This ▮▮▮▮ Hispanic male was hospitalized approximately 1.5 years into the study (437 days after the New-Fill treatment session) for Dupuytren type lesion with retraction of the fifth digit. The patient was hospitalized for surgery to resolve the condition. This patient also reported ten other AEs of moderate to mild intensity. The patient continued in the study and completed all visits.

Arteriovenous fistula operation (Patient): This ▮-year-old Caucasian male was hospitalized for implantation of arteriovenous fistula due to chronic renal insufficiency, at approximately 9 months into the study (244 days following the first New-Fill treatment session). The SAE was considered by the investigator as not related to the treatment device. Patient had five other AEs during this study, 4 mild and one moderate; all but one mild intensity AE (nocturnal cramps) resolved, and the patient received an additional 5th treatment session 39 days after the onset of the SAE, and subsequently completed the study.

Anemia folate deficiency (Patient): This ▮-year-old Caucasian male was hospitalized due to anemia that was secondary to a Malocine (pyrimethamine) induced folate deficiency 42 days after the last injection session of New-Fill, and the condition eventually resolved. The SAE was considered to be not related to the New-Fill treatment by the investigator. The patient had a history of cerebral toxoplasmosis and Kaposi's disease. The patient also had seven other AEs; all of those except one (increased transaminase values) resolved. The patient completed the study.

Skin ulcer (Patient): This ▮-year-old Caucasian male was hospitalized (for an unspecified time) due to a persistent ulcer (x 3 years) of the right internal malleolus more than one year following the last injection session of New-Fill, and the condition remained ongoing at the end of the study. The SAE was considered unrelated to New-Fill. The patient completed the study. One other AE of mild intensity (subcutaneous nodules on the right and the left cheeks) was reported.

Lymphoma (Patient): This ▮-year-old Caucasian male was diagnosed and hospitalized on 09/10/2002 with a severe, high-grade, large cell lymphoma. This SAE occurred 483 after the last injection session of New-Fill. Although the SAE was considered unrelated to the study treatment, the patient withdrew from the study prematurely. Accordingly, data for this patient are available for up to Week 48. This patient also reported two other mild intensity AEs, which were not related to the device, and resolved within 4 weeks.

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Study of the Impact of Intradermal Polylactic Acid

Genian Implants in HIV-Seropositive Patients

with Severe Facial Lipoatrophy

A Single-Center Open Pilot Study

Principal Investigator

Clinical Coordination

Dermatological Coordination

Methodology & Statistics

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SCIENTIFIC COUNCIL

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VEGA

ABSTRACT

The purpose of this study is to evaluate the effect and tolerance of intradermal injections of polylactic acid (Newfill®) into the cheeks and temples of HIV-infected patients on effective antiretroviral therapy who have developed severe facial lipoatrophy.

1 - OBJECTIVES

Principal Objective
To evaluate the increase in genian skin thickness after three intradermal polylactic acid injections in patients exhibiting lipoatrophy on antiretroviral therapy.

Secondary Objectives
- To evaluate the immediate tolerance of these injections.
- To study the long-term evolution of the injected areas (effect on and tolerance by the dermis).

2 - METHODOLOGY

A single-center, non-comparative, open, pilot study.

3 - ELIGIBILITY CRITERIA

Inclusion Criteria
- Age > 18 years
- Patient seropositive for HIV
- Viral load (VL) < 5000 cp/ml for more than 3 months
- Current antiretroviral therapy started at least 3 months earlier
- Antiretroviral therapy initiated at least 3 years earlier
- Genian subcutaneous adipose tissue measured by ultrasonography < 2 mm

Non-Inclusion Criteria
- Clinical disease under investigation or in the acute phase of treatment
- Plans to be at a distant location or on a long trip during the first two months of the study
- Noncompliance and/or irregular follow-up
- Facial dermatological condition incompatible with the tested therapy
- Facial Kaposi's sarcoma
- Injection of a filling agent into the face during the previous six months
- Active labial herpes
- Ongoing interferon therapy
- Pregnant or nursing woman

4 - STUDY DIAGRAM

· Patients with marked facial lipoatrophy,
defined by a thickness of the genian subcutaneous tissue < 2 mm
measured by ultrasonography
↓

D0, D15, D30
Bilateral intradermal injections
1 vial of Newfill® = 0.15 g of polylactic acid = 3 ml
↓

D45
Measurement of thickness of dermis
If < 8 mm, injection No. 4
↓

M3, M6, M12, M18, M24
Clinical, ultrasound and laboratory follow-up

5 - ASSESSMENT CRITERIA

6 - DURATION OF STUDY
24 months

7 - TOTAL NUMBER OF PATIENTS
50 evaluable patients

8 - COMMENCEMENT OF STUDY
May 2000

2 - INTRODUCTION AND JUSTIFICATION OF STUDY

Recent advances in antiretroviral therapy combining inverse transcriptase inhibitors and protease inhibitors have made it possible to achieve potent inhibition of HIV replication in many patients. This brings about an increase in CD4 number, which in turn is responsible for a major decrease in the prevalence of opportunistic infection and a prolongation of survival (1).

However, several publications and many clinical observations attest to a lipodystrophy syndrome that complicates these therapies over the relatively long term in a large number of patients. This partial or generalized lipodystrophy syndrome is characterized by a change in the distribution of subcutaneous and perivisceral adipose tissue, and can be associated with abnormalities of lipid and glucose balance, particularly increases in triglycerides and the development of a resistance to insulin (2-7). Although there is currently no consensual definition of lipodystrophy, it is most often described in three clinical forms: lipoatrophy, central adiposity, and a mixed form combining peripheral lipoatrophy and central adiposity.

Lipoatrophy is characterized by the loss of Bichat's fat pads; atrophy of the retro-orbital adipose tissue; atrophy of the subcutaneous adipose tissue of the limbs, causing a decrease in the volume of the arms, thighs and buttocks; and relative venomegaly.

Central adiposity is characterized by an increase in the volume of the breasts and abdomen and the potential accumulation of subcutaneous fat on the posterior aspect of the base of the neck, a condition known as buffalo hump. This clinical form can be associated with hematologic abnormalities of lipid and glucose metabolism (8,9).

In the most recent studies, the prevalence of lipodystrophy in HIV-seropositive individuals receiving antiretroviral therapy is about 60% (10-12). The prevalence of the various clinical forms varies from one study to the next, however. Central adiposity has been estimated at 14% in an Australian study (12), while in the French studies APROCO (10) and LIPOSUD (11), it is between 30 and 40%. The mixed form is estimated at 55% in the Cooper study, versus 25% and 32% in the APROCO and LIPOSUD studies. Finally, the incidence of lipoatrophy is stable in these three studies, at around 30%.

There seems to be a link -- although this has not been clearly established -- between clinical form and type of antiretroviral therapy. For example, patients treated with protease inhibitors apparently more often develop a central form that is usually associated with glycolipid abnormalities (10).

A number of factors are also associated with a greater likelihood of developing lipodystrophy: age, sex, ethnic origin, duration of HIV infection, duration of exposure to therapeutic drugs, especially d4T, and changes in body mass index (5,13,14).

There is currently no explanation for this syndrome, although various physiopathological theories have been advanced.

The clinical expression of this syndrome can be so pronounced that compliance with antiretroviral therapy may be compromised. The severity of the lipoatrophy can have heavy psychological and social repercussions, especially when the face is affected, since involvement of the adipose panniculus in that area can cause profound and manifest facial wasting.

These phenomena can signify severe progressive disease to an outside observer and are a major source of distress to the affected individual. The changes in the legs and arms are easy to conceal; the facial changes are not.

Given the lack of a clear physiopathogenic explanation for these abnormalities, and since no etiologic therapy has been clearly shown to be effective, an attempt at a palliative, symptomatic therapeutic approach to offer relief to these patients is indicated. In effect, changes in compliance with proposed antiretroviral therapies may alter the immunovirologic prognosis of patients who find themselves in this situation.

There are already several palliative approaches used to fill the subcutaneous adipose compartment for cosmetic purposes.

Fat autografting by the Collman method consists in removing adipocytes from the abdominal subcutaneous tissue. After ultracentrifugation, the cells are reimplanted under the dermis of the lipoatrophied area. This technique is troublesome, however, requiring general anesthesia for puncture of the abdominal fat. Furthermore, the reimplanted tissue would disappear with a kinetics close to that of the onset of the original lipoatrophy. Finally, and most important, this procedure cannot be used in some patients because they lack a sufficient abdominal adipose panniculus.

Non-biodegradable synthetic implants, silicone being chief among them, entail the disadvantage of potential immediate or late allergic reactions and the establishment of inflammatory granulomas with a possible

rejection reaction (15).

Other techniques utilize biodegradable implants. These are implants either of animal origin, such as collagen, which carries the risk of allergic reactions in 2 to 3% of cases, or of biological origin, such as hyaluronic acid, which is resorbed especially rapidly, in a few weeks to a few months (16-19).

Newfill® is a hydrogel of polylactic acid (PLA), a biocompatible, biodegradable, immunologically inert synthetic polymer.
PLA has been used for several years in many therapeutic applications as resorbable suture material in ophthalmologic, neurologic and thoracoabdominal surgery. In traumatology, materials for osteosynthesis and ligament repair have been made from this molecule. Finally, PLA is widely used in maxillofacial surgery, in periodontology and in stomatology, primarily as a substrate for tissue regeneration in the treatment of bone defects (20-23).

PLA is widely used in cosmetic procedures, especially for filling wrinkles. It was approved for this indication by the G-MED (Groupement européen d'homologation des dispositifs médicaux [European Group for the Certification of Medical Devices][1]) on November 30, 1999.

The loss of adipose tissue observed in lipoatrophy syndrome is, a priori, a possible indication for these skin filling procedures. Polylactic acid causes an increase in skin thickness both directly, by its volume alone, and indirectly, by the local fibroblastic reaction and neocollagenesis which it triggers.
Preliminary results in ten patients show that three to four injections into the genian tissue are

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[1]TRANSLATOR'S NOTE: Properly the Groupement européen d'évaluation des dispositifs médicaux, the European Group for the Evaluation of Medical Devices.

accompanied by a median increase of about 7 to 10 mm in the thickness of the dermis. The immediate tolerance seems to be excellent. Current follow-up is 3 to 6 months.

Several questions arise with regard to subcutaneous implants in lipoatrophic, HIV-seropositive individuals:
- What is the immediate tolerance of this technique?
- What is the durability of the effect obtained?
- Over the long term, is there any local toxicity to the dermis in the implanted area?

To alleviate this serious situation, which is being experienced by an increasing number of patients, we propose to carry out a pilot study in 50 patients exhibiting severe facial lipoatrophy, evaluating the potential benefit of genian filling with Newfill® implants for one month, with a 24-month follow-up period to examine tolerance and durability.

3 - OBJECTIVES

3.1 - Principal Objective
To evaluate the increase in total genian skin thickness (TST) after intradermal polylactic acid injection in patients exhibiting severe lipoatrophy on antiretroviral therapy.

3.2 - Secondary Objectives

- To evaluate the immediate and late tolerance of Newfill® injections: is there a temporary or prolonged change in the structure of the dermis subsequent to this treatment?
- To evaluate the durability of the effect of these injections.

4 - METHODOLOGY

This will be an open, non-comparative, single-center pilot study. The follow-up period per patient is 24 months; the planned inclusion period is 6 months.

5 - ELIGIBILITY CRITERIA

5.1 - Inclusion Criteria

- Age > 18 years
- Patient seropositive for HIV
- HIV plasma viral load < 5000 cp/ml for more than 3 months
- Current antiretroviral therapy started at least 3 months earlier
- Antiretroviral therapy initiated at least 3 years earlier
- Genian subcutaneous adipose tissue measured by ultrasonography < 2 mm

5.2 - Non-Inclusion Criteria

- Clinical disease under investigation or in the acute phase of treatment
- Plans to be at a distant location or on a long trip during the first two months of the study
- Noncompliance and/or irregular follow-up
- Facial dermatological condition incompatible with the tested therapy
- Facial Kaposi's sarcoma
- Injection of a filling agent into the site during the previous six months
- Active labial herpes
- Ongoing interferon therapy
- Pregnant or nursing woman

6 - STUDY DIAGRAM

Screening: D-14

Patient exhibiting marked facial lipoatrophy,
defined by a thickness of the genian subcutaneous adipose tissue < 2 mm
measured by ultrasonography

↓

D0
Injection No. 1, intradermal, on both sides
1 vial of Newfill® = 0.15 g polylactic acid = 3 ml

↓

D15
Injection No. 2

↓

D30
Injection No. 3

↓

D45
Measurement of thickness of dermis:
if < 8 mm → injection No. 4

↓

M3, M6, M12, M18, M24
Clinical, laboratory and ultrasound follow-up

7 - ASSESSMENT CRITERIA

7.1 - Principal Criterion

Measurement of the increase in total skin thickness (TST) at M6.

7.2 - Secondary Criteria

- Evaluation of the percentage of patients who are "responders" at M6, M12, M18, M24. Any patient whose total skin thickness is ≥ 10 mm will be classified as a "responder."
- Self-evaluation based on a visual analog scale (VAS) of overall well-being.
- Evaluation of immediate and delayed tolerance.

8 - STUDY PROCEDURE

8.1 - Pre-inclusion

After the informed consent has been signed, the pre-inclusion assessment will be performed on D-14, including:

- Clinical examination, VAS
- Standard laboratory panel
- CD4-CD8 lymphocytes, HIV viral load (dating from less than three months earlier)
- Blood lactates
- Ultrasound genian examination
- Photographs, if possible including any taken before the onset of the lipoatrophy.

8.2 - Treatment and Follow-Up

8.2.1. - Injection Procedures

- The injections will be performed by the dermatological coordination team at each visit: multisite injection of a total of 3 ml of polylactic acid hydrogel (i.e., 0.15 g) into the middle dermis of the area to be treated.
- The injections will be bilateral at D1, D15 and D30, with a possible time lag of 15 days.

- A fourth injection may be indicated if the thickness of the dermis measured 15 days after the third injection remains less than 8 mm.
- If major temporal atrophy is present, additional injections will be offered for administration at separate times from the genian injections.
- The injections will be postponed if transient facial skin lesions should develop.

The treatment will be discontinued in the event of a poorly tolerated immediate local reaction or at the request of the patient.

8.2.2 - Evaluation at D45:

- VAS
- NFS, platelets, transaminases, cholesterol, triglycerides as per the antiretroviral therapy received.
- Ultrasonography: if the measured overall skin thickness remains less than 8 mm, a fourth injection may be offered.
- Photographs.

8.2.3 - Follow-up: at M3, M6, M12, M18 and M24

- Clinical examination
- VAS
- NFS, platelets, transaminases, cholesterol, triglycerides as per the antiretroviral therapy received.
- CD4-CD8 lymphocytes
- Plasma HIV viral load
- Lactate assay (M6)
- Ultrasonography of the cheeks, and photographs (except at M3)

8.3 - Duration of Study

The study duration is 24 months, in order to determine the tolerance of the treatment well after the procedure.

8.4 - Commencement of Study

May 2000

8.5 - Total Number of Patients

Enrollment will continue until 50 evaluable patients have been included in the study.

9 - RADIOLOGIC EVALUATION

9.1 - Ultrasound Follow-Up

For uniformity of evaluation, the evaluation will be performed by one practitioner using a single apparatus in order to maximize the reproducibility of the results.

Radiologic investigator: ███████████████████

The radiologic evaluation of the skin will be performed by ultrasonography, and its purpose will be to measure in precise and reproducible fashion the three components of this tissue from surface to depth: the epidermis, the dermis and the subcutaneous adipose panniculus.

This examination will include exploration of:
- depressed areas of the skin (genian and temples)
- changes in the polylactic acid implant
- the onset and course of any neovascularization of the kind that has been described in contact with polylactic acid microspheres.

At screening the principal radiologic inclusion criterion will be checked, i.e., a subcutaneous adipose panniculus of 2 mm or less.

At D45, M6, M12, M18 and M24: measurement of the thickness of the dermis and evaluation of local neovascularization.

9.2 - Equipment Used

The technician will use a latest-generation, multifrequency, digital-digital probe type of sensor covering frequencies of 7.5 to 13 mHz (the type of sensor used in examination of the thyroid and all superficial areas).

The images of the sections taken will be stored on some type of data medium, i.e., diskettes, zip disks, etc. (but will include the maximum possible number of sections of the involved areas to permit easy and reproducible selection at a later time).

The acquisition of the paper-medium photographic images will be performed in a uniform and reproducible manner on a single Mitsubishi thermal sublimation color printer.

9.3 - Ultrasound Examination Technique

To obtain a sharp, easy-to-interpret and reproducible image of the three components of the skin, attention will be given to:

- spreading the area concerned with a film **of at least 1 cm of gel**, to be replenished as needed during the examination;
- scanning the area **as lightly as possible** to prevent any measurement distortion due to "crushing" of the skin in the area under examination;
- recording **transverse and longitudinal** images of the area.

9.4 - Localization of Areas To Be Examined

- For shallow and deep **"genian depressions"**: bilateral localization will be performed by taking up a position anatomically anterior to the masseter, centered on the region of the buccinator, using the malar region as the upper landmark. Areas having a "median skin fold" will not be taken into account, since the presence of such a fold might falsify future interpretation. (These areas will not be filled.)

- For **"temporal depressions,"** which may be involved due to individual upward prolongations of the Bichat's fat pad, bilateral localization of the temporal region alone will be performed by delimiting the area based on the bony landmarks of the orbital arch anteriorly and the zygomatic process inferiorly.

9.5 - Evaluation of Ultrasound Data

- Measurements will be taken, from surface to depth, of the thickness of the epidermis, the dermis and the subcutaneous adipose panniculus, expressed in mm.

- The ultrasound examination will indicate whether or not there is any particular vascularization of the dermis or transient neoangiogenesis.

- Atypical prolongations of the parotid gland can extend, sometimes very superficially, into the region where the nasopalatine canal opens into the cheek, and such prolongations will be looked for in order to avoid injuring them during the injections.

9.6 - Evaluation of Photographs

A group of three independent observers will meet every three to six months, depending on the state of advancement of the trial, to refine the evaluation of the cosmetic benefit of the Newfill® injections.

10 - STATISTICAL METHODS

10.1 - Number of Patients

It is hoped that the percentage of subjects showing satisfactory results (total skin thickness ≥ 10 mm) at W24 will be 80%, and that it can be shown to be significantly higher than 60%. Given a risk α of 0.05 and a power of 90% and using a chi-square test, it will therefore be necessary to enroll 50 evaluable subjects.

10.2 - Statistical Analysis

The statistical analysis will describe the included patients in terms of demographic, clinical and facial lipoatrophy data. The main assessment criterion will be analyzed by means of a chi-square test; the percentage of responders and the 95% confidence interval at each phase of evaluation will also be calculated. Similarly, the variation of total skin thickness will be calculated in each patient for each phase, together with the mean and the confidence interval of this parameter. The course of the HIV infection will also be described, as will all adverse events, whether related or unrelated to the procedure.

-17-

11 - ETHICAL CONSIDERATIONS

███████ Law

███
███
███████████████████████████████

11.2 - Data Collection

The monitoring will be performed by the physicians of the coordination team (█████████████████) under the responsibility of ███ in ███████ in accordance with the rules of good clinical practice. The center's physician investigators will be responsible for completing the case logs after each visit. The forms intended for the case log will be sent to the statistical methodology center, ██████████████████████████ St

11.3 - Center Participating in the Study

██

11.4 - Data Confidentiality

The case logs and the laboratory reports prepared in connection with this study will be stored in a locked room. The data will be accessible only to a limited number of individuals responsible for the study investigation. The data files will be created in compliance with the Computers and Freedom Law.

11.5 - Scientific Council

The clinical trial is under the responsibility of the Scientific Council. The function of the Council is to settle problems of a scientific, methodological and ethical nature raised by the trial. It will render decisions as to the continuation of the trial, given the data and any other information that may justify altering the course of the study. The Council will meet once every six weeks for the first three months to evaluate the conduct of the trial. It may also be convened by the investigators.

The Scientific Council see to the release of information to all participants and will ensure compliance with the rules governing publication of the results.

The Scientific Council is composed of the following persons:

- ███████████
- ████████████ er
- ████████████
- I███████████
- ██████████
- ██████████████

11.6 - Sponsor of Study

██
██

11.7 - Insurance

██
██
████████████████████

The insurance policy was taken out with ████████████████████████
████████████████████████

12 - BIBLIOGRAPHIC REFERENCES

[Translation of foreign-language entries:]

15. Faure, M., "Complications of implants made of silicone and other reputedly inert materials," *Ann. Dermatol. Venerol. 122* (1995), 455-459.

17. Pons-Guiraud, A., "Delayed hypersensitivity reactions to bovine collagen implants. A study in 810 patients," *Nouv. Dermatol. 11* (1992), 422-432.

19. Velly-Mores, "First attempts to fill wrinkles with hyaluronic acid," *Nouv. Dermatol. 16* (1997), 186-189.

ANNEXES

VEGA: FOLLOW-UP SCHEDULE

	Screening D-14	D0	D15	D30	D45	M3	M6	M12	M18	M24
Inclusion criteria	☒									
Clinical examination	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒
VAS	☒				☒	☒	☒	☒	☒	☒
Laboratory:										
- Standard assessment	☒				☒	☒	☒	☒	☒	☒
- CD4-CD8	☒					☒	☒	☒	☒	☒
- HIV viral load	☒					☒	☒	☒	☒	☒
- Lactates	☒						☒			
Injection		☒	☒	☒	☒ If TST ≤ 8 mm [Note 2]					
Photographs	☒ (+ prior photos [Note 1])				☒	☒	☒	☒	☒	☒
Facial ultrasound	☒				☒	☒	☒	☒	☒	☒

[1] Collection of any photographs taken before the onset of lipoatrophy.

[2] TST = total skin thickness; if a fourth injection is given, an additional visit must take place at M2, comprising a clinical examination, the VAS and standard laboratory tests.

VISUAL ANALOG SCALE (VAS)
FOR EVALUATION OF "OVERALL WELL-BEING"

In the column headed QOL (vertical Quality of Life scale), indicate how you feel physically and psychologically by placing a horizontal bar at the level you consider to correspond to your general status. The 0 to 10 graduation is intended merely as a frame of reference.

Date: |_| |_|/ |_| |_|/ |_| |_|

	QOL	
- For "satisfactory" status, the better you feel, the higher the number.	10	**6 to 10** = satisfactory physical and/or emotional status
		5 = okay
- For "unsatisfactory" status, the worse you feel, the lower the number.		
	0	**0 to 4** = unsatisfactory physical and/or emotional status

CISIH PITIE SALPETRIERE

Department of Infectious and Tropical Diseases
Clinical Research Unit

V
E
G
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CASE REPORT FORM

Patient No.

Patient Code

Patient No.	Preinclusion Visit	D-14
Patient Code	Date	

Participation consent

Informed consent signed   yes__   no__

Epidemiological data

Date of birth:

Sex: Male__   Female__

Ethnic origin: Caucasian__   Hispanic__   North African__

                  Caribbean__   Black Africa__   Asian__

Clinical, biological and therapeutic history

CLINICAL HISTORY

Date of seropositivity:

CDC stage: A__   B__   C__   1__   2__   3__

Date of the first AIDS event:

MORPHOLOGICAL MODIFICATIONS

			Emergence date
• Melting of Bichat's fat pads	yes	no	
• Atrophy of the upper limbs	yes	no	
• Atrophy of the lower limbs	yes	no	
• Modification of the venous network	yes	no	
• Buffalo hump	yes	no	
• Increase in breast volume	yes	no	
• Increase in abdomen circumference	yes	no	
• Other:	yes	no	

Patient No.	Preinclusion Visit	D-14
Patient Code	Date	

BIOLOGICAL HISTORY

CD4 nadir: ___/mm3 ___% date:
Viral Load Zenith: ___copies/ml date:

ANTIRETROVIRAL THERAPY HISTORY
(a molecule is considered to have been received if actually taken for at least one month)

	Antiretroviral Treatments	Month/Year
1		from / to /
2		from / to /
3		from / to /
4		from / to /
5		from / to /
6		from / to /
7		from / to /
8		from / to /
9		from / to /
10		from / to /
11		from / to /
12		from / to /

Patient No.	Preinclusion Visit	D-14
Patient Code	Date	

Clinical Examination

Weight: ___.__ kg   Baseline weight: ___.__kg   Height: ___cm

Karnofsky's Index: ___%   Temperature: ___.__°

Examination

- Cardiac   __Normal   __Abnormal
- Pulmonary   __Normal   __Abnormal
- Digestive   __Normal   __Abnormal
- Neurological   __Normal   __Abnormal
- Skin   __Normal   __Abnormal
- Other   __Normal   __Abnormal

Comments:

"Global well-being" Visual Analogical Scales

Scale filled out: yes__   no__   date:

(Enclose copy of the scale filled out)

Current Treatment

Start date ___/___/___

NRTI		**IP**	**NNRTI**
AZT: __	CBV: __	SQV: __	NVP: __
D4T: __	ABV: __	RTV: __	EFV: __
DDI: __	ADF: __	IDV: __	DLV: __
DDC: __		NFV: __	
3TC: __		AMP: __	HU: __

Patient No.	Preinclusion Visit	D-14
Patient Code	Date	

ANTIRETROVIRAL TREATMENT COMPLIANCE
Number of intakes forgotten during the last week

Comments:

ASSOCIATED TREATMENTS
Fill out the continuous data form provided for this purpose

Biology

Lymphocytes CD4: ____/mm3 ___%   date __/__/__
Must be at least 3 months prior to D-14

Viral load: _____ copies/ml   date __/__/__
VL must < 5,000 cp/ml for more than 3 months   *Must be at least 3 months prior to D-14*

Standard Biology: Normal__   Abnormal__

If abnormal, nature of abnormalities:

Lactacidemia: __.__ mmol/l   date __/__/__

Morphological examinations

1 – ECHOGRAPHY: date __/__/__
2 – DOPPLER   date __/__/__

Results: *enclose a copy of the internal data sheet*

3 – PHOTOGRAPHS: Taken   yes__ no__   date __/__/__

Photographs before the emergence of lipodystrophy to be collected to the extent possible, if available: date __/__/__

| Patient No. | Preinclusion Visit | D-14 |
| Patient Code | Date | |

ELIGIBILITY CRITERIA

1 – Age > 18 years   __yes   __no
2 – Patient HIV seropositive   __yes   __no
3 – Viral load less than 5,000 copies/ml for more than 3 months   __yes   __no
4 – Current antiretroviral treatment started for at least 3 months   __yes   __no
5 – Antiretroviral treatment started for at least 3 months   __yes   __no
6 – Subcutaneous genian fatty tissue less than 2 mm measured by ecography   __yes   __no

NON-ELIGIBILITY CRITERIA

1 – Clinical condition under investigation or in acute treatment phase   __yes   __no
2 – Traveling far or for a long time scheduled in the first two months of the study   __yes   __no
3 – Patient non-compliant and/or with irregular follow-up   __yes   __no
4 – Face skin condition incompatible with the treatment tested   __yes   __no
5 – Face Kaposi's sarcoma   __yes   __no
6 – Injection with a filling product in site within the last 6 months   __yes   __no
7 – Ongoing lip herpes   __yes   __no
8 – Ongoing treatment with Interferon   __yes   __no
9 – Pregnant or breast-feeding woman   __yes   __no

Patient No.	Visit D ___ / M ___
Patient Code	Date

Clinical Examination

Weight:
Modifications since the last visit: Yes___ No___
If yes, detail of the clinical examination:

- Cardiac   ___Normal   ___Abnormal
- Pulmonary   ___Normal   ___Abnormal
- Digestive   ___Normal   ___Abnormal
- Neurological   ___Normal   ___Abnormal
- Skin   ___Normal   ___Abnormal
- Other   ___Normal   ___Abnormal
- Morphological modifications   Yes___   No___

Modification type:

CLINICAL EVENTS WHICH TOOK PLACE SINCE LAST VISIT   Yes___ No___

Comments:

"Global well-being" Visual Analogical Scales

Scale filled out: yes___ no___   date:
(Enclose copy of the scale filled out)

Morphological examinations

1 – ECHOGRAPHY: date ___/___/___
2 – DOPPLER   date ___/___/___

Results: *enclose a copy of the internal data sheet*

3 – PHOTOGRAPHS: Taken   yes___ no___   date ___/___/___

Patient No.	Visit D ___ / M ___
Patient Code	Date

Antiretroviral treatment

COMPLIANCE

Number of intakes forgotten during the last week:

Comments:

MODIFICATIONS IN ANTIRETROVIRAL TREATMENT   Yes__ No__

Reason for the modification:

Nature of the modification: *fill out the continuous data sheet provided for this purpose*

Associated Treatments

Modification in associated treatments: yes__   no__
If yes, fill out the continuous data sheet provided for this purpose

---

Biology

Lymphocytes CD4: ____/mm3   __%   date __/__/__

Viral load: _____ copies/ml   date __/__/__

Standard Biology: Normal__   Abnormal__

If abnormal, nature of abnormalities:

Lactacidemia: __.__ mmol/l   date __/__/__

Patient No.	
Patient Code	Date

PREMATURE FOLLOW-UP STOPPAGE FORM

      Date of premature treatment stoppage   __/__/__

	Grade III or IV undesirable event
	Death Date of death __/__/__
	Patient's choice
	Investigator's judgment: *specify*
	Drop-out patient (missed two consecutive visits)
	Date of last visit __/__/__
	Other: *specify*

Signature of the investigator: Date __/__/__

| Patient No. |
| Patient Code |

CLINICAL AND/OR BIOLOGICAL UNDESIRABLE EVENTS

Clinical event (diagnosis or symptoms) and/or biological event (one per line)	Start date	Severity (grade) 1=mild 2=moderate 3=severe 4=life-threatening	Consequences		Link 0=Undetermined 1=Unrelated 2=Doubtful 3=Possible 4=Probable 5=Certain	Measures taken		Severe undesirable effects N=no O=yes
			R=resolved N=non-resolved F=fatal	Resolution date of the symptoms or infection or death		with treatment studied 0=None 1=Dose reduction 2=Treatment suspended 3=Final treatment suspension X=Without application	Symptomatic treatment N=no O=yes If yes, specify the treatment in the column "associated treatments"	
1.	/ /			/ /				
2.	/ /			/ /				
3.	/ /			/ /				
4.	/ /			/ /				
5.	/ /			/ /				
6.	/ /			/ /				
7.	/ /			/ /				
8.	/ /			/ /				

Patient No.		
Patient Code		Date

SEVERE UNDESIRABLE EVENTS – ADDITIONAL DATA

Date of birth ___/___/___	Sex	_male female	Weight ___.___ kg	Time interval between the latest intake of treatment and the beginning of symptoms day or hours		
Product studied:	Dose	Units	Frequency	Administration path	Start date / /	Stoppage date / /

What is the severity of the undesirable event?		What is the cause of this event?	
__ 1. Death __ 2. Immediate threat to life __ 3. Hospitalization __ 4. Biological abnormalities or significant clinical event (grade 3 or 4)	__ 5. Invalidity or disability __ 6. Overdose __ 7. Cancer __ 8. Congenital abnormality __ 9. Pregnancy	__ 1. Treatment studied __ 2. Inefficacy of treatment __ 3. Abandonment of treatment __ 4. Concomitant treatment: *specify*	__ 5. Associated disease: *specify* __ 6. Other: *specify*

Brief description of clinical symptoms, treatments, evolution and biological results that may explain this event:

Significant medical and surgical history 1. 2. 3.	Date / / / / / /
If the patient died, cause of death:	Date: ___/___/___ Autopsy? __no __yes

Investigator: Address Signature:	Date: / /

Patient No.
Patient Code

ASSOCIATED TREATMENTS

Commercial name (one per line)	Start date	End date	Administration path and dose	Indication
1.	/ /	/ /		
2.	/ /	/ /		
3.	/ /	/ /		
4.	/ /	/ /		
5.	/ /	/ /		
6.	/ /	/ /		
7.	/ /	/ /		
8.	/ /	/ /		
9.	/ /	/ /		
10.	/ /	/ /		

| Patient No. |
| Patient Code |

CONTINUOUS RECORD OF MODIFICATIONS IN ANTIRETROVIRAL TREATMENT

Molecule (Commercial name or abbreviation)	Start date	End date	Dose (dose in mg x number of intakes/d)		Reason for stoppage or comments
1.	/ /	/ /	x	/D	
2.	/ /	/ /	x	/D	
3.	/ /	/ /	x	/D	
4.	/ /	/ /	x	/D	
5.	/ /	/ /	x	/D	
6.	/ /	/ /	x	/D	
7.	/ /	/ /	x	/D	
8.	/ /	/ /	x	/D	
9.	/ /	/ /	x	/D	
10.	/ /	/ /	x	/D	

| Patient No. |
| Patient Code |

ECHOGRAPHY and DOPPLER (Liaison form)

Date	Thickness of the dermis (mm)		Thickness of the fat (mm)		Observations
	R	L	R	L	
D-14 / /					
D45 / /					
M6 / /					
M12 / /					
M18 / /					
M24 / /					
Additional visit / /					

| Patient No. |
| Patient Code |

ECHOGRAPHY and DOPPLER (Liaison form)

Date	Thickness of the dermis (mm)		Thickness of the fat (mm)		Observations
	R	L	R	L	
/ /					
/ /					
/ /					
/ /					
/ /					
/ /					
/ /					

Patient No.		
Patient Code	Date	

END OF STUDY FORM

- Did the patient stop the study prematurely?   __No   __Yes
If yes, fill out the form "reason for premature follow-up stoppage"

- Was the patient reached during the 24 months of follow-up?   __No   __Yes

---

I the undersigned Doctor , certify the exactness of the information entered into the book.

In

Signature

date __/__/__

Stamp of the department

Patient No.
Patient Code

EVALUATION OF POLYLACTIC ACID INJECTIONS

Visit		During injection		Comments
		Quantity of PLA injected	Technical problems encountered	
D0 1st injection	Right cheek			
	Left cheek			
D15 2nd injection	Right cheek			
	Left cheek			
D30 3rd injection	Right cheek			
	Left cheek			
D45	Right cheek			
	Left cheek			
M3	Right cheek			
	Left cheek			
M6	Right cheek			
	Left cheek			
M12	Right cheek			
	Left cheek			
M24	Right cheek			
	Left cheek			

Patient No.
Patient Code

EVALUATION OF POLYLACTIC ACID INJECTIONS

Visit		During injection		Comments
		Quantity of PLA injected	Technical problems encountered	
Additional injection Date	Right cheek			
	Left cheek			
Additional injection Date	Right cheek			
	Left cheek			
Additional injection Date	Right cheek			
	Left cheek			
Additional injection Date	Right cheek			
	Left cheek			
Additional injection Date	Right cheek			
	Left cheek			
Additional injection Date	Right cheek			
	Left cheek			
Additional injection Date	Right cheek			
	Left cheek			
Additional injection Date	Right cheek			
	Left cheek			

Sponsor: ███████████████

CLINICAL STUDY REPORT

A Randomized Open-Label Study of Polylactic Acid (New-Fill®) Injections for Buccal Fat Pad Wasting in Persons with HIV-Related Lipoatrophy

Investigators: ██████████████

Study Site: ████████████████████

Date first patient was enrolled: 15 June 2001
Date last patient completed the study: 15 March 2002

Report type: Original report

INVESTIGATOR STATEMENT:

I certify that, in my capacity as Principal Investigator of this study, I believe to the best of my knowledge, that all data and information submitted in this report are truthful and accurate and that no material fact has been omitted.

_____   _____
                                                                Date

Date of issue: 07 NOVEMBER 2003   VERSION 1.0

11-002

STUDY SYNOPSIS

Study short title　███████████████ New-Fill for the Treatment of Facial Lipoatrophy

Title: A Randomized Open Label Study of Polylactic Acid (New-Fill®) Injections for Buccal Fat Pad Wasting in Persons With HIV-Related Lipoatrophy

Investigator, study site: ███████████████████████████████████,

Study duration and dates:　June 2001 to March 2002

Objectives: This study was intended to evaluate the use of polylactic acid injections in an immediate versus delayed study design to enable assessment of both immediate (12 week) and prolonged (24 week) effects.

Study design: Randomized, open label, comparative (2 group), single-centre

Number of patients planned: 30

Main inclusion criteria: HIV positive patients with moderate to severe buccal (naso-labial area and cheeks) fat pad loss. Patients had to be willing and able to provide informed consent, not pregnant or lactating, and using adequate contraception as appropriate.

Treatment procedures: Three deep dermal facial injection sessions in the buccal area with New-Fill® (PLLA) at intervals of two weeks, commencing either at study entry (Immediate Group) or 12 weeks after entry into the study (Delayed Group). The rationale for the study design was to provide a control group for comparative purposes whilst ultimately treating all study patients.

Effectiveness data: The clinical endpoints were buccal skin thickness as assessed by ultrasound, change in appearance, assessed by Visual Analogue Scale (VAS) scores, and anxiety and depression scores, at Weeks 12 and 24.

Safety data: Safety was assessed by means of change in viral load and CD4 cell counts, changes in blood chemistry parameters, and adverse events.

Anxiety and Depression Scores: Anxiety and depression were assessed using the validated Hospital Anxiety and Depression Scale.

11-003

Statistical procedures: p-values were based on the t-test for continuous variables, the chi-square test for discrete variables and the Wilcoxon Rank-sum test for non-parametric variables, as appropriate. All statistical tests were two-sided with a significance level of 0.05. Ultrasound dermal thickness, anxiety and depression scores and visual analog scores were analyzed by comparing the changes from baseline to Week 12 and Week 24 between the two treatment groups.

Results - Study patients and conduct: 30 patients were entered into the study and all 30 patients completed the trial. Data are presented for 29 of these patients; one patient (B10) was not included in this report due to privacy issues.

Results – Safety: A total of 24 (83%) patients reported one or more treatment-emergent adverse events. The most common adverse event was injection site bruising [11 (38%) patients] followed by skin nodules [9 (31%] patients].

Seventeen (59%) patients experienced one or more treatment-related adverse events. All episodes of injection site bruising and skin nodules were considered by the Investigator to be treatment-related. Other common treatment-related events were injection site discomfort [3 (10%) patients], injection site inflammation [3 (10%) patients], and injection site erythema [3 (10%) patients].

One episode of treatment-related injection site bruising was severe. This was associated with the first injection and the patient did not experience further severe adverse events. All other treatment-related adverse events were mild or moderate. There were no serious adverse events.

There were no statistically significant or clinically meaningful differences between the groups or changes from baseline in any laboratory values, including CD4 cell counts and viral load.

Results – Effectiveness:

Dermal Thickness (mm)	Immediate Group N=14 Weeks 12 and 24			Delayed Group N=8 Week 12, N=13 Week 24			Between-Group p-value
	Baseline Mean	Change from Baseline Mean (SD)	Within-Group p-value	Baseline Mean	Change from Baseline Mean (SD)	Within-Group p-value	
Left Naso Labia							
Week 12	2.4	3.9 (2.1)	<0.001	2.4	0.1 (0.6)	0.774	<0.001
Week 24	2.5	5.3 (1.8)	<0.001	2.4	5.7 (2.1)	<0.001	0.525
Right Naso Labia							
Week 12	2.7	4.3 (2.9)	<0.001	2.3	0.2 (0.7)	0.448	0.001
Week 24	2.7	4.9 (2.3)	<0.001	2.5	6.0 (2.6)	<0.001	0.250
Left Cheek							
Week 12	2.4	4.1 (2.8)	<0.001	2.1	0.4 (0.4)	0.037	0.001
Week 24	2.5	4.9 (1.8)	<0.001	2.3	5.7 (1.8)	<0.001	0.247
Right Cheek							
Week 12	2.6	3.9 (2.4)	<0.001	2.3	0.3 (0.4)	0.121	<0.001
Week 24	2.6	4.9 (2.3)	<0.001	2.4	5.5 (2.3)	<0.001	0.487

Significant values (p <0.05) are bolded.
Source Data: Table 21, 21OCT03 – V_FINAL, CHGULTRA/V_TABLE2_1/ V_TABLE2_1

11-004

Significant changes from Baseline (p<0.001) in dermal thickness were observed in the areas treated with New-Fill (left and right naso labia and cheeks) at Week 12 and maintained through Week 24 in the Immediate treatment group. Significant changes from baseline were not observed until Week 24 (i.e., 12 weeks after initiation of treatment) in the Delayed Group (p<0.001), thus, the patients in the Delayed Group acted as a negative control to the Immediate treatment group at the Week 12 time point. A mean increase in dermal thickness of approximately 4-5 mm was observed twelve weeks after the initiation of treatment for both the Immediate Group (Week 12), and in the Delayed treatment group (Week 24). Areas that were not treated with the product failed to show improvements in dermal thickness at any time point and therefore acted as an internal control.

As expected, differences in dermal thickness at treated sites were significantly different between groups at Week 12 (p<0.001). No differences between groups in dermal thickness were observed at Week 24 of therapy, indicating that the treatment is effective regardless of initiating treatment immediately or delaying treatment.

Similar to the dermal thickness observations above, significant improvements in self-assessment visual analogue scores of the face were observed at Weeks 12 and 24 in the Immediate Group and at Week 24 in the Delayed Group.

Results – Anxiety and Depression Scores: Mean (SD) HAD anxiety scores decreased from Baseline by 2.7 (4.6) in the Immediate Group (p<0.05) at Week 12, and by 2.5 (3.6) at Week 24 (p<0.05). At Baseline, mean HAD anxiety scores were within the range "suggestive of mood disorder" and the decreases brought the mean scores within the range of "normal". Although there was positive change in anxiety score compared with Baseline at Week 24 in the Delayed Group [-2.5 (4.5)] the difference was not statistically significant (p=0.072).

Mean (SD) HAD depression scores decreased by 1.9 (3.4) in the Immediate Group (p<0.05) at Week 12, and by 2.1 (4.2) at Week 24 (p=0.070). There was a significant improvement in HAD depression scores at Week 24 in the Delayed Group [-2.8 (4.2), p<0.05] but not at Week 12. There was no significant difference between the two groups at either time point.

Conclusions

- Treatment with a course of three injection sessions of New-Fill® (PLLA) was associated with a significant increase in skin thickness in the treatment area within 12 weeks of administration regardless of whether patients were treated immediately or if treatment was delayed by 12 weeks. This increase was still evident at 24 weeks after initiation of treatment in the Immediate Group.

- The treatment-related adverse events observed were consistent with the method of administration (deep dermal injections).

- Injections of New-Fill (PLLA) was found to be an efficacious and safe method of increasing facial thickness in HIV positive patients presenting with the signs of facial lipoatrophy.

11-005

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END-OF-TEXT FIGURES

N/A

11-011

LIST OF LISTINGS

Listings located in Appendix C.1.

11-012

ABBREVIATIONS AND DEFINITIONS

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAART	Highly Active Anti-Retroviral Therapy
HAD	Hospital Anxiety and Depression scale
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
IEC	Independent Ethics Committee
IND	Investigational New Drug
LDL	Low Density Lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
n	Number of patients
nos	Not Otherwise Specified
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PI	Protease Inhibitor
PLLA	Poly-L-lactic acid (New-Fill®)
SAE	Serious Adverse Event
SD	Standard Deviation
VAS	Visual Analogue Scale

11-013

1 INTRODUCTION

The introduction of potent antiretroviral regimens (highly active antiretroviral therapy, HAART) has dramatically changed the natural history of human immunodeficiency virus (HIV)-1 infection. However, as these regimens do not eradicate HIV infection, therapy is currently considered life-long.

Short-term therapy with antiretroviral agents has been associated with an increase in body weight and an improvement in nutritional status of HIV-1 infected patients. Longer-term (>1 year) therapy has been associated with negative metabolic derangements and effects such as new-onset diabetes mellitus, hyperlipidaemia, and abnormal body fat distribution (also called lipodystrophy).

The pathogenesis of these metabolic and clinical phenomena remains speculative. No definitive management is established.

Reported clinical manifestations of lipodystrophy have not been homogeneous and range from central or localized adiposity to peripheral fat wasting. Patients with peripheral fat wasting frequently present with increased vein prominence as well as loss of facial fat pads such as the temporalis and naso-labial (also called Bichat's or buccal) fat pads. As the naso-labial fat pad lies in the communication triangle between the eyes and the mouth it is the most overtly stigmatizing effect of lipodystrophy. The impact of loss of this fat pad is substantial, affecting social functioning, employment, sexual function and self-esteem.

Poly-L-lactic acid (PLLA) injections (New-Fill®) represent a new form of cosmetic 'filler' which provides for appearance improvement through both an initial bulk effect and subsequent stimulation of fibroblasts to increase collagen production. Anecdotal evidence from France (Dr. Amard study)[1] suggests that it may be beneficial in managing the loss of the naso-labial fat pad. No comparator-controlled study of PLLA has been performed but New-Fill® is approved by the devices evaluation agency in the UK.

This study was undertaken in order to evaluate the use of PLLA injections in an immediate versus delayed study design to enable assessment of both immediate (12 week) and prolonged (24 week) effects. The study was designed so that a treated cohort of patients (Immediate Group) could be compared with an untreated cohort (Delayed Group) at Week 12. This study design allowed for the ethical treatment of all patients who needed it, while allowing a comparison of treated and untreated patients after 12 weeks. ███████████████████████████████████████ Commercially available product was used for the trial.

██ All data were monitored and verified retrospectively after obtaining authorization from ████████ patients entered into the study by a contract research organization (████████████). One patient in the Delayed Group (B10) specifically stated that they did not want their data to be used; therefore, the data for this patient are not reported. For the remaining ████ patients, anonymous, unverified data were included in the analysis. The ███████████████ conducted analysis of patient data and assisted in the preparation of this report.

11-014

2   IDE CONDUCT

2.1   INDICATION OF IDE STATUS

This study was run independently by the clinical investigator in ██████████████ nd was not conducted under a United States Investigational Device Exemption (IDE).

2.2   APPLICABILITY OF FOREIGN DATA TO US POPULATION

Similar antiviral treatment is used for the treatment of HIV in Europe and the US. Since there appears to be a link between HIV-related antiretroviral therapy and lipodystrophy, the results of this study would have application both in Europe and in the US.

2.3   ETHICS

2.3.1   Independent ethics committee

The study protocol, and the Patient Information Sheet and Consent Form were submitted to an independent ethics committee (IEC), the ██████████████ nd received a favorable opinion on 7 June 2001. Appendix A.1.5 contains the Ethics Committee approval letter.

Appendix A.1.5 contains the name and affiliations of the members of ██████████████

2.3.2   Patient information and informed consent

Written, informed consent was obtained from each patient. However, some study related assessments that were taken prior to the patient's participation in the study were occasionally used. Appendix A.1.4 contains a sample informed consent document.

Retrospectively, an "Informed and voluntary consent to the collection, processing and usage of personal data" form was signed by ███ f the 30 patients authorizing release of the data obtained in this study to Dermik Laboratories, for use in a regulatory application for the product. Data for the ███ patients who gave consent were monitored and verified retrospectively by ██████████████ n behalf of Dermik Laboratories after obtaining authorization. One patient ████ specifically stated that they did not want their data to be used. For the remaining two patients, anonymous, unverified data were included in the analysis. Therefore, the data set for this study includes a total of 29 patients: 15 in the Immediate Group and 14 in the Delayed Group.

11-015

2.4 PROTOCOL, AMENDMENTS AND ADMINISTRATIVE CHANGES

The Investigator submitted the protocol to the IEC for review and approval (Appendix A.1.1). The "Informed and voluntary consent to the collection, processing and usage of personal data" consent form for the follow-up were submitted to the IEC on 24 February 2003, and approved on 4 March 2003 (Appendix A.1.4).

2.5 ADMINISTRATIVE STRUCTURE

Details of the personnel who worked on the study, and their role, are given below:

11-016
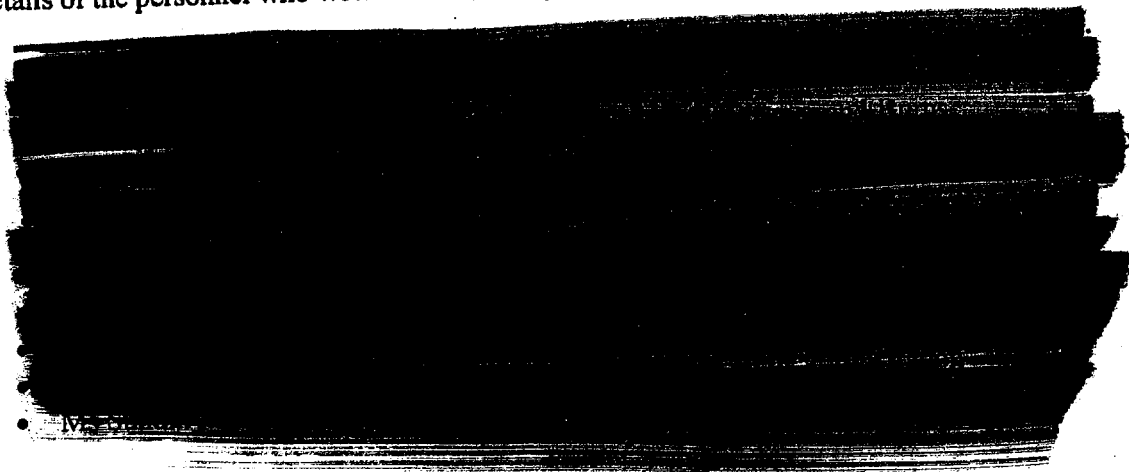
3   CLINICAL STUDY METHODS

3.1   OVERALL STUDY DESIGN

This study was a randomized, open label, comparative (2 group), single-centre, study. Although all patients received facial PLLA injections at 2 week intervals, the treatment was administered at entry into the study in half of the patients (Immediate Group) but 12 weeks after entry for the remaining patients (Delayed Group), thus enabling efficacy comparisons to be made during the first 12 weeks of the study while maintaining the ethical integrity of the study.

3.2   CLINICAL ENDPOINTS

- Buccal skin thickness measurement as assessed by ultrasound at Week 12 and Week 24.
- Perception of body thinness assessed by Visual Analog Scale (VAS).
- Change in viral load and CD4 cell count.
- Questionnaire (Anxiety and depression rating).
- Change in blood chemistry parameters.
- Adverse events.

3.3   COLLECTION OF ADVERSE EVENTS

Adverse events were collected at each study visit and again at the Recall Visit, approximately 2 years after study completion. Patients were asked an open-ended question about their health.

The Ethics Committee required the investigator to report immediately any serious adverse events that were considered to be related to the study product. FDA SAE reporting procedures were not applicable because the trial was not run under an IDE. It should be noted that no SAEs were reported by any patients during the conduct of the trial.

3.4   TIME COURSE OF OBSERVATIONS/FOLLOW-UP

Patients were initially screened for eligibility to enter the study and gave their consent to participate. Their participation commenced on Day 1, which was up to one week after the screening visit. Randomization was performed after completion of all the assessment procedures.

Patients in the Immediate Group received bilateral injections of PLLA on Day 1. These injections were repeated two weeks and four weeks later. Patients in the Delayed Group received bilateral PLLA injections 12 weeks, 14 weeks and 16 weeks after entry into the study. Assessments were made at Weeks 12 and 24. Approximately two years from the patient's baseline visit (i.e., 1 to 1.5 years after the completion of the study), patients returned to the clinic to gain their consent for retrospective data verification and for further discussion about their experience with the product.

11-017

During this recall visit, more information was obtained but the data are of limited value because the time of the visit since Baseline was variable and the data were uncontrolled.

3.5 DURATION OF STUDY – START TO FINISH

Patients were recruited to the study over a period of 3 months and were followed up for 24 weeks. The overall duration of the study was therefore 36 weeks (9 months), from June 2001 to March 2002.

3.6 CLINICAL SIGNIFICANCE

The clinical endpoints for the study as outlined in the protocol, were:

- Buccal skin thickness measurement as assessed by ultrasound at Week 12 and Week 24.
- Perception of body thinness assessed by VAS.
- Change in viral load and CD4 cell count.
- Anxiety and depression rating.
- Change in blood chemistry parameters.
- Adverse events.

3.7 STATISTICAL HYPOTHESIS

3.7.1 Effectiveness Hypothesis

No hypothesis testing was specifically stated in the protocol; however, based upon the design of the trial, the null hypotheses tested were 1) there is no difference between clinical endpoints for the Immediate and Delayed treatment groups at Week 12, and 2) there is no difference between clinical endpoints at baseline and the post-baseline visits (Week 12 and Week 24).

3.7.2 Evaluation of Safety Results

The safety of the study treatment was evaluated by analysis of reported adverse events.

3.8 SAMPLE SIZE CALCULATION FOR NUMBER OF PATIENTS AND ITS BASIS

A total of 30 patients were recruited into the study, 15 patients into each treatment group.

This was an open-label pilot study. No sample size calculations were initially performed to assess the number of patients required to achieve statistical power. However, a sample size estimate was requested by the Ethics Committee and was prepared subsequently.

11-018

For the purpose of this study, the following assumptions were made. In a normal population, the thickness of the dermis ranges from 1.1 mm to 4 mm. The midpoint of these figures can be used to estimate the average thickness of dermis in a normal population: 2.6 mm.

Mean thickness of dermis in normal population

Normal   Lipoatrophy

Normal value of dermis   **Abnormal** value 1.3 mm.
2.6 mm
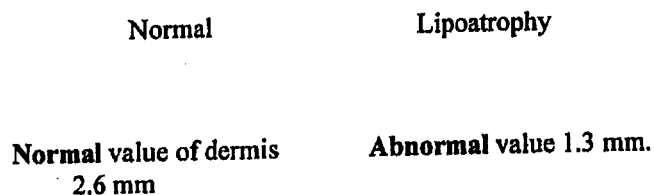
Assuming the distribution of dermis measurements would be normally distributed, an increase in thickness of the dermis measurement by 50% from baseline was assumed to describe patients with success in treatment.

Thickness of dermis (mm)		Standard deviation of paired difference	Power	Significance level (2-sided)	Total no. of patients required
Lipoatrophy	Normal				
1.3	2.6	2.0	90%	5%	28
1.3	2.6	2.0	80%	5%	22

Assuming that the thickness of the dermis data would be normally distributed with pooled standard deviation of 2.0 mm, detecting a difference of change in the dermis by 50% from baseline with 90% certainty and 5% significance level, the total sample required would be 30 patients. This assumed that the patients recruited were unlikely to dropout.

3.9   STUDY PATIENT POPULATION

3.9.1 Number of Patients

A total of 30 patients were recruited into the study, and 15 patients were randomized into each treatment group.

11-019

3.9.2 Inclusion Criteria

Patients meeting all of the following criteria were considered for enrollment into the study:

1. HIV positive.
2. Physician and patient agreed moderate to severe naso-labial fat pad loss.
3. Willing and able to provide informed consent.
4. Not pregnant or lactating. Using adequate contraception as appropriate.

3.9.3 Exclusion Criteria

Patients meeting any of the following criteria were not included in the study:

1. Active opportunistic disease or wasting syndrome.
2. Planned plastic surgery.
3. Current growth hormone therapy.
4. Oral hypoglycemic therapy or lipid lowering agent commenced within one month.
5. Current chemotherapy for malignancy.
6. Known hypersensitivity to PLLA.

3.10   STUDY PROCEDURES AND SCHEDULE

3.10.1 Description of Study Visits

A summary of the determinations performed at each study visit is provided in Table 1 at the end of this section.

Screening

Prior to the study, patients were screened for eligibility to enter the study and suitable patients signed a consent form.

Demographic data (gender, age and race) were collected. A clinical examination was performed but the findings were not recorded for the purpose of the study.

Protease Inhibitor (PI) and Nucleoside Reverse Transcriptase Inhibitor (NRTI) experience was recorded and fasting blood samples were collected for measurement of laboratory variables including high and low density cholesterol, triglycerides, liver function tests, lactate, insulin, glucose, CD4 cell count and HIV viral load.

Day 1 - Study Entry

On Day 1 of the study, up to one week after the screening visit, a clinical examination was performed (although the findings were not documented), and fasted blood samples were collected for measurement of laboratory variables including fasting high and low density cholesterol, triglycerides, liver function tests, lactate, insulin, glucose, CD4 cell counts and HIV viral load.

11-020

Facial ultrasound was carried out to assess skin thickness and patients were asked to assess their perception of thinness of their face, arms, legs, abdomen, and buttocks using 10 cm VAS. One end of the VAS was preprinted as "as thin as it/they has/have ever been" with an assigned value of "0", and the other end was denoted as "not at all thin" with an assigned value of "10". HAD scales were completed by each patient and facial photographs were taken for assessment of facial changes by a team of assessors. Eligible patients were then allocated randomly into either the Immediate Group or the Delayed Group.

Treatment Visits

After completion of all assessment procedures, patients in the Immediate Group received bilateral injections of PLLA on Day 1. These injections were repeated two weeks and four weeks later.

Patients in the Delayed Group received bilateral PLLA injections 12 weeks, 14 weeks and 16 weeks after entry into the study.

Weeks 12 and 24

At Week 12 and Week 24, the following procedures were repeated:
- A clinical examination was performed, though the findings were not documented.
- Fasted blood samples were collected for measurement of laboratory variables including CD4 cell counts and HIV viral load.
- Facial ultrasound was carried out to assess skin thickness.
- Patients assessed their perception of thinness of their face, arms, legs, abdomen, and buttocks using VAS.
- HAD questionnaires were completed by each patient.
- Facial photographs were taken for assessment of facial changes by a team of assessors.

Patients were assessed for adverse events at all visits to the clinic after the Baseline visit.

Recall Visit

Approximately two years from the patient's baseline visit (i.e., 1 to 1.5 years after the completion of the study), patients were recalled for a follow up visit that was not part of the original protocol. During this unscheduled visit, patients were asked for their authorization to utilize their data from this study in a submission to the FDA. For those patients who agreed, their data were retrospectively validated and discrepancies were corrected and verified. In addition, HAD and VAS scores were completed and any adverse events that had occurred between the end of the study and the follow up visit were recorded.

The collection and use of the HAD and VAS scores and the follow-up comments from the Recall Visit were not formally approved of by the ethics committee, however the patients were informed and agreed to this follow-up visit at the time of re-consent.

11-021

Table 1: Schedule Of Assessments

Time point	Screening	Baseline Day 1	Week 2	Week 4	Week 12	Week 14	Week 16	Week 24	Recall Visit[1]
									✓
Consent	✓								
Demography	✓								
PI/NRTI experience	✓								
Clinical examination[2]	✓*	✓*			✓			✓	
Serum biochemistry[3]	✓*	✓*			✓			✓	
Facial Ultrasound	✓*	✓*			✓			✓	
Viral Load	✓*	✓*			✓			✓	
CD4 Cell Count	✓*	✓*			✓			✓	
HAD Questionnaire	✓*	✓*			✓			✓	✓
VAS	✓*	✓*			✓			✓	✓
Injections Immediate Group		✓	✓	✓					
Injections Delayed Group					✓	✓	✓		
Adverse Events Immediate Group		✓	✓	✓	✓	✓	✓	✓	✓
Adverse Events Delayed Group		✓	✓	✓	✓	✓	✓	✓	✓
Photography	✓*	✓*			✓			✓	

[1] Not part of the original protocol; [2] Clinical examination findings were not documented, [3] Including fasting high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol, triglycerides, liver function tests, lactate, insulin and glucose). *Could have been performed at either visit.

3.10.2 Methods

Ultrasound Facial Skin Thickness

Ultrasound recordings of the face were performed on Day 1 and at Weeks 12 and 24.

Ultrasound was performed by one radiologist, to maximize the reproducibility of the results obtained. A Seimens Elegra ultrasound machine with a linear array transducer and a 13.5 MHZ variable frequency probe was used for ultrasound measurement. A hard copy of the examination results was taken and an EXCEL spreadsheet of the results was produced.

Measurements of skin thickness were made perpendicular to the skin surface at the nasolabial fold, corner of the mouth, zygomatic arch, and centrally between these points in the buccal fat pad area. Generous gel contact was made with the probe to avoid skin compression. Three measurements were made and the most reproducible measurement was recorded.

11-022

Measurement of skin thickness was derived from the ultrasound recordings for the following treated regions:

- Left naso labia.
- Right naso labia.
- Left cheek.
- Right cheek.

And also for the following untreated (control) regions:

- Left mouth.
- Right mouth.
- Left zygoma
- Right zygoma.

Recording of Perception of Body Shape by Visual Analogue Scale

Patient perceived changes in body shape were assessed using a visual analogue scale that was designed for the study and completed on Day 0 and at Weeks 12 and 24. A copy of the VAS scale can be found in Appendix A.1.3.

Patients were asked to separately record their perception of the thinness of their face, arms, legs, abdomen and buttocks as an intercepting line on a 10 cm linear scale labeled 'as thin as it/they has/have ever been' at one end, and 'not at all thin' at the other. The results were translated into numbers potentially ranging from 0 to 10 by measuring the distance from the left hand edge of the scale to the line marked by the patient.

Hospital Anxiety and Depression Scores (HADs)

HADs were completed by the patients on Day 1 and at Weeks 12 and 24. The HAD is a standard reference tool that is used routinely in hospitals in the UK to evaluate depression and anxiety[2]. A copy of the HAD Scale 1 can be found in Appendix A.1.3.

Facial Photography

Photographs of patients' faces were taken on Day 1 and at Weeks 12 and 24. The data were analyzed by the Investigator and were not validated by Dermik.

At the end of the study, photographs were assessed in random order using the following facial lipodystrophy picture scale:

- 0= normal
- 1= mild.
- 2= moderate
- 3=severe

11-023

Supportive diagrams and example photographs were provided to assist evaluation that had been specifically designed for the study. Assessors scored the aspect of the buccal fat pad above and below the zygomaticus major muscle and the temporalis extension of fat pad, which lies inferior to the zygoma over the masseter muscle. As the temporalis area was untreated, this acted as an internal control.

The validation set for clinical photograph evaluation was assessed by three clinic doctors not involved in the study, three medical students and three lay individuals. These data indicated that visual assessment scoring of photographs was reproducible and that scores for each photograph were similar between medical assessors but less similar or reproducible for lay assessors. The kappa statistics for all nine assessors indicated a moderate to good agreement between individual scores performed 2 weeks apart (kappa = 0.53, p=0.157). Excluding the three lay assessors, a good to very good agreement was achieved (kappa statistics 0.65, p=0.083). Scoring of photographs of the total population was, therefore, undertaken using only the three clinic doctors as assessors[3].

Adverse Events Reporting

Adverse events were collected throughout the study and were recorded at each visit during the study. Adverse events were elicited in response to an open-ended question.

3.11 USE OF DEVICE

3.11.1 Device Description

New-Fill is a skin implant in the form of a sterile apyrogenic suspension, which is reconstituted from a sterile dry powder by the addition of sterile water for injections. This suspension contains micro-particles of Poly-L-Lactic Acid, the crystalline form of P.L.A. It is a synthetic polymer, is biocompatible, biodegradable, and immunologically inert.

To reconstitute the product, slowly add 3ml of water to the dry powder and let it stand for at least 20 minutes (do not shake) to ensure that the powder dissolves. Shake until a homogeneous translucent suspension is obtained. It is then ready for use. (New-Fill® [Package Insert]. Luxembourg: Biotech Industry S.A.; 2002.)

3.11.2 Treatment Procedures

For each treatment session, 0.15 g of PLLA was reconstituted by the addition of 2 ml of sterile water for injection and 1 ml of 2% lidocaine to give a total volume of 3 ml.

Up to 3 ml of the reconstituted PLLA hydrogel was injected into multiple points into the deep-dermis of the treatment area (buccal region) on each side of the face. Following injection, the skin was massaged to ensure better distribution of the gel.

Individual details of the reconstitution and administration of the injection are provided in Listing 6 (Appendix C.1).

11-024

3.12 WITHDRAWAL AND REPLACEMENT PROCEDURES

No replacement procedures for patients that withdrew prematurely were specified in the protocol.

3.13 QUALITY ASSURANCE AND QUALITY CONTROL

3.13.1 Data quality assurance

Full hospital records were kept for each patient, in keeping with routine clinical practice. Demography, PI and NRTI experience, photographic assessment scores, ultrasound data, CD4 cell counts, viral loads, triglycerides, glucose, cholesterol (HDL and LDL), lactate, insulin, HAD score totals for anxiety and for depression, and VAS measurements were entered onto EXCEL spreadsheets by a single operator.

Printouts of the EXCEL spreadsheets and additional data collected by study site personnel on a "Data Collection Sheet" were verified by ▬▬▬▬▬ (for those patients who gave their consent) and transferred to ▬▬▬▬▬. These data were stamped as certified copies/originals and signed by the site personnel. All Data Collection Sheets were single data-entered into EXCEL. The final EXCEL datasets were converted by▬▬▬▬ Data Management Department into SAS version 6.12 datasets. QC was performed on the data originally collected in EXCEL as a 100% point-to-point comparison of the SAS datasets to the EXCEL spreadsheets to verify that all data was converted to SAS correctly. Additionally, a 100% point-to-point comparison of the SAS datasets to the Data Collection Sheet was performed. To check for any data entry errors as well as to ensure the conversion to SAS was correct, QC was also performed on the datasets after any updates, additions, and coding were completed.

3.13.2 Monitoring and auditing

Since this study was not originally intended for registration purposes, the trial was not internally or externally monitored during the conduct of the study. However, for the ▬▬patients who gave their consent to utilize their data in the FDA submission, retrospective verification against the available source documentation was performed by a monitor from the contract research organization, the ▬▬▬▬▬ In order to keep patient data confidential, the site assigned each patient a unique number based on the treatment group to which they were assigned. Patients in the Immediate Group were assigned A1, A2, etc, and patients in the Delayed Group were assigned B1, B2, etc. A decode list is maintained by the site.

▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬

11-025

Moreover, an audit was performed by ████████████████████ t and an Audit Certificate is provided in Appendix A.4.4.

A quality control check of the database (100%) was performed prior to database lock.

11-026

4 STATISTICAL AND ANALYTICAL PROCEDURES

4.1 STUDY VARIABLES

The study variables were:

- Ultrasound facial skin thickness.
- Perception of body shape by VAS.
- HAD.
- Adverse events.

4.2 STATISTICAL METHODOLOGY

The ▮▮▮▮▮▮▮▮ retrospectively analyzed these data in order to duplicate the original analyses of the investigators using the cleaned and validated data. An "Informed and voluntary consent to the collection, processing and usage of personal data" form was signed by ▮▮ f the 30 patients authorizing release of the data obtained in this study to Dermik Laboratories, for use in a regulatory application for the product. Data for the ▮▮ atients who gave consent were monitored and verified retrospectively after obtaining authorization. ▮▮ Therefore, the data set for this study includes a total of 29 patients: 15 in the Immediate Group and 14 in the Delayed Group.

Data were analyzed using SAS statistical software. All statistical tests were two-sided with a significance level of 0.05.

Baseline Information

Baseline continuous parameters such as age were summarized for each treatment group by the number of patients with non-missing values (n), the mean and standard deviation, the median, the minimum value, and the maximum value. Categorical parameters such as gender were summarized by the number and percentage of patients in each category. P-values were based on the t-test for continuous variables and the chi-square test for discrete variables. Descriptive summaries of medical history and concomitant medications were provided showing the number of patients and percentages for each medical history term or concomitant medication term.

11-027

Efficacy Information

Parameter Descriptions

One radiologist took all ultrasound measurements. The measurements of skin thickness were made perpendicular to the skin surface at the nasolabial fold, corner of the mouth, zygomatic arch, and centrally between these points in the buccal fat pad area. Three measurements were made and the most reproducible measurement was recorded. Measurements of skin thickness were derived from the ultrasound recordings for the following treated regions: left naso labia, right naso labia, left cheek, and right cheek. Measurements were also derived for the following untreated (control) regions: left mouth, right mouth, left zygoma, and right zygoma.

The Hospital Anxiety and Depression Scale assessed anxiety and depression. This was measured on a scale from 0-21, where 0-7= Normal Range, 8-10= Suggestive of the presence of the mood disorder, and 11-21= Probable presence of the mood disorder. Since low values indicate a better score than high values, a positive change indicates worsening whereas a negative change indicates improvement.

Visual analog scores were based on a scale from 0-10, where 0: As Thin As It Has Ever Been and 10: Not At All Thin. For this scale, since lower scores are less desirable, a positive change indicates improvement whereas a negative change indicates worsening (except for the waist assessment, which would be less desirable to have a fatter waist indicating a potential progression of the disease).

Analysis

The changes from baseline to Week 12 and Week 24 in ultrasound dermal thickness measured in millimeters were displayed for the following facial areas: left naso labia, right naso labia, left mouth, right mouth, left zygoma, right zygoma, left cheek, and right cheek. For each treatment group, the following information was displayed: the number of patients with non-missing change values, the baseline mean, the treatment mean, the mean change from baseline and standard deviation, the minimum and maximum changes, and the within-group p-value based on the 1-sample t-test. The two treatment groups were compared for each facial area and the p-value based on the 2-sample t-test as well as the non-parametric p-value based on the Wilcoxon Rank-sum test were both displayed.

The changes from baseline to Week 12 and Week 24 in the anxiety and depression scores were summarized descriptively and statistically in the same manner as described above for the ultrasound dermal thickness.

The changes from baseline to Week 12 and Week 24 in the visual analog scores were displayed for the following areas of the body: face, arms, legs, bottom, and waist/abdomen. These scores were summarized descriptively and statistically in the same manner as described above for the ultrasound dermal thickness.

11-028

Safety Information

The laboratory parameters CD4 (cells/µl), Triglycerides (mmol/l), Glucose (mmol/l), Cholesterol HDL (mmol/l), Cholesterol LDL (mmol/l), Total Insulin (mU/l), Lactate (U/l), ALT (U/l), AST (U/l), Bilirubin (mg/dl), and Alkaline Phosphatase (IU/l) were summarized. Displayed in the tables for Week 12 and Week 24 were the number of patients with non-missing values, the baseline mean, the treatment mean, the mean change and standard deviation, the minimum and maximum change from baseline values, and the within-group p-value based on the 1-sample t-test. The two treatment groups were compared for each laboratory parameter and the p-value based on the 2-sample t-test as well as the non-parametric p-value based on the Wilcoxon Rank-sum test were both displayed.

Viral load (copies/ml) was summarized at Baseline, Week 12, and Week 24 by the categories: <50 and ≥50. For each category, the number and percentage of patients were displayed for each treatment group as well as the p-value based on the Chi-Square Test.

Treatment emergent adverse events were displayed by system organ class and MedDRA term. For each event, the number and percentage of patients in each treatment group having the event were displayed. Summaries include classifications by intensity (mild, moderate, or severe) and relationship to treatment (yes or no). Serious adverse events and adverse events that were related to treatment were also displayed. For further details of statistical methods, please refer to Appendix B.1.

11-029

5   RESULTS – STUDY PATIENTS AND CONDUCT

5.1   NUMBER OF INVESTIGATORS AND PATIENTS PER INVESTIGATOR

There was one investigational site and one Principal Investigator for this study (shown below).

The site enrolled a total of 30 patients. All 30 patients completed the study.

5.2   DEMOGRAPHICS AND BASELINE CHARACTERISTICS

5.2.1   Demographics and Patient Characteristics

Data were available for 15 patients in the Immediate Group and 14 in the Delayed Group. One patient did not give consent for their data to be included in the report.

The two groups were generally well matched with respect to demographic details at baseline (Table 2). Most (93%) of the patients were male, with mean age of about 41 years and 72% of the total were Caucasian. Patients in both groups had been on PI therapy for approximately 3 years and on NRTI therapy for 6 to 7 years. CD4 cell counts were slightly below 500 cells/mm^3 in both treatment groups. There was no significant difference between the groups with respect to any of the above demographic details (p>0.05).

There was a significant difference between the groups with respect to viral load: median viral load was 72.0 copies/ml in the Immediate Group and 0.0 copies/ml in the Delayed Group (p=0.012). However, this difference is not considered clinically relevant.

More summary demographic information is provided in Table 1.1 (Section 9) and full details for each patient are provided in Listing 1 (Appendix C.1).

11-030

Table 2: Demographic Details

Demography	Immediate Group N=15		Delayed Group N=14	
Age (years) mean (SD)	41.5	(5.5)	40.7	(7.7)
Gender (n, %)				
Male	14	(93%)	13	(93%)
Female	1	(7%)	1	(7%)
Race (n,%)				
Caucasian	10	(67%)	11	(79%)
Hispanic	5	(33%)	2	(14%)
Black	0		1	(7%)
PI experience (months) mean (SD)	36.1	(19.1)	41.1	(20.8)
NRTI experience (months) mean (SD)	82.2	(27.0)	77.6	(35.1)
CD4 Cell Counts (mm^3) mean (SD)	466	(155)	482	(207)
HIV Load (copies/ml) median (range)	72.0 (0.0 to 126794)		0.0 (0.0 to 12189)*	

* p=0.012
Source Data: Table 1.1, 21OCT03 - FINAL, DEMOG/V_TABLE_1_1/V_TABLE_1_1

5.2.2 Medical History

Eight (53%) patients in the Immediate Group and seven (50%) patients in the Delayed Group had lipodystrophy and/or hyperlipidaemia reported on their medical history.

One patient in the Immediate Group had a history of anxiety, one patient in this group had a history of panic attacks, and one patient in the Delayed Group had a history of anxiety with panic attacks. Two patients in the Immediate Group and two in the Delayed Group had a history of depression.

More summary information on medical history is provided in Table 1.2 (Section 9). Individual patient details are given in Listing 7 (Appendix C.1).

5.3 ACCOUNTABILITY AND POOLABILITY

5.3.1 Accountability

All of the 30 patients randomized completed the 24 weeks of the study. Data for one patient (B10) are not included in this report for the US FDA due to privacy issues; however, data from this individual were included in the original poster presentation of the data (refer to Appendix A.6).

5.3.2 Data Poolability

Not applicable since this was a single center study.

5.4 PROTOCOL DEVIATIONS

[text redacted]

5.5 ADMINISTRATION OF DEVICE

5.5.1 Treatment Assignment

Patients were randomized sequentially to either the Immediate treatment group or the Delayed treatment group at the time of consent signing. A randomization schedule is provided in Appendix A.3.1

5.5.2 Treatment and duration

All patients received three treatment sessions, approximately two weeks apart, of New-Fill® PLLA (Table 1.4, Section 9). One vial of product (3 cc) was injected into each cheek at each session.

5.5.3 Compliance

All treatments were administered by a single plastic surgeon, [redacted]. Therefore patients were deemed to be 100% compliant.

5.5.4 Product Accountability

The product is freely available as a marketed product licensed for use as a "wrinkle-filling agent". Study supplies were not provided to the Investigator by a pharmaceutical company.

11-032

All product was supplied to the site by ███████████████████████ All patients received product from the same lot numbe██████████ The pharmacy received and dispensed the product to the treating physician on a visit-by-visit basis. A copy of the Certificate of Analysis is provided in Appendix A.3.3.

5.6 PATIENT DISCONTINUATIONS/DEATHS

There were no withdrawals from the study for any reason. No patients died during the study.

5.7 CONCOMITANT MEDICATIONS

The most common concomitant medications taken by the patients in this study were NRTIs (Table 3). Every patient in the study took one or more concomitant medication and the two groups were balanced with respect to the class and frequency of the medications.

A full summary of concomitant medication is provided in Table 1.3 (Section 9) and details for each patient are given in Listing 8 (Appendix C.1).

Table 3: Summary of Most Common (Taken by >10% of Patients) Concomitant Medications

Class Medication	Immediate Group N=15		Delayed Group N=14	
Antiviral (n, %)				
Aciclovir	1	(7%)	3	(21%)
Non-NRTI (n, %)				
Efavirenz	6	(40%)	9	(64%)
NRTI (n, %)				
Abacavir	6	(40%)	5	(36%)
Didanosine	4	(27%)	3	(21%)
Lamivudine	10	(67%)	9	(64%)
Stavudine	9	(60%)	10	(71%)
Tenofovir	1	(7%)	2	(14%)
PI (n, %)				
Nelfinavir	1	(7%)	3	(21%)
Ritonavir	2	(13%)	1	(7%)
Saquinavir	2	(13%)	1	(7%)
Miscellaneous (n %)				
Amoxicillin	2	(13%)	1	(7%)
Canesten-HC	2	(13%)	4	(29%)
Loperamide	3	(20%)	1	(7%)
Oilatum Emollient	2	(13%)	1	(7%)
Paramol 118	1	(7%)	2	(14%)
Vitamins	4	(27%)	2	(14%)

Source Data: Table 1.3, 23OCT03 – FINAL, CONMEDS/V_CONMED/0_CONMED

11-033

6 SAFETY AND EFFECTIVENESS DATA

6.1 INDIVIDUAL SAFETY DATA

Adverse event data are provided in Listings 9.1 and 9.2 and chemistry laboratory results are in Listing 5 (Appendix C.1).

6.2 INDIVIDUAL EFFECTIVENESS DATA

Individual VAS scores are given in Listing 2, HAD scores in Listing 3 and ultrasound dermal thickness in Listing 4 (Appendix C.1).

6.3 DEVICE FAILURES AND REPLACEMENTS

No problems with the device were reported.

6.4 PATIENT COMPLAINTS

No patient complaints were reported during the study, although the Investigator did not actively solicit this information. During the Recall Visit (not part of the original study), patient comments were captured by the site personnel (refer to Listing 12 in Appendix C.1). In general, some patients were still pleased with the results even after one year; however, many of the patients either expressed an interest in re-treatment or had paid for additional treatments after the study was completed. Comments from patients at the Recall Visit revealed the following:

- Eight patients noted that they were pleased or happy with the original results of the New-Fill treatment and 6 still remained pleased. The other 2 patients felt that the original effects were beginning to wane.

- Fourteen patients had additional treatment(s) after the study was completed. The average number of re-treatments was 4.7 (range 1 to 17) with one patient not reporting the number of additional treatments. Additionally one patient was treated with Bio-Alcamid in another country and was happy with the result.

11-034

7 RESULTS OF STATISTICAL ANALYSIS FOR CLINICAL INVESTIGATION

7.1 SAFETY

7.1.1 Adverse Events

Overview of Adverse Events

Twelve (80%) patients in the Immediate Group and twelve (86%) patients in the Delayed Group reported one or more treatment emergent adverse events (Table 4). The incidence of individual adverse events was low, with the most frequently reported adverse events relating to administration of the study treatment. The most common adverse event was injection site bruising [11 (38%) patients] followed by skin nodules [9 (31%) patients].

Four (3%) patients in the Immediate Group and eight (57%) patients in the Delayed Group reported one or more adverse events after signing consent but prior to any study treatment. Individual non-treatment emergent adverse events are given in Listing 9.2 (Appendix C.1).

Summary information on treatment-emergent adverse events is provided in Table 3.3 (Section 9). Individual adverse events are given in Listing 9.1 (Appendix C.1).

Table 4: Summary of Most Common (Reported by >10% Patients) Adverse Events

System Organ Class MedDRA Term	Immediate Group N=15	Delayed Group N=14	Combined Groups N=29
Overall (n, %)	12 (80%)	12 (86%)	24 (83%)
Gastrointestinal (n,%)			
Diarrhoea	3 (20%)	0	3 (10%)
General & Administration Site (n,%)			
Injection site bruising	7 (47%)	4 (29%)	11 (38%)
Injection site discomfort	2 (13%)	1 (7%)	3 (10%)
Injection site erythema	3 (20%)	0	3 (10%)
Injection site inflammation	0	3 (21%)	3 (10%)
Injection site nodule	6 (40%)	3 (21%)	9 (31%)
Investigations (n,%)			
Weight decreased	2 (13%)	1 (7%)	3 (10%)

Source Data: Table 3.3, 30OCT03 – V_FINAL, AETAB1/V_AEINTEN/ 0_AEINTEN

11-035

Intensity of Adverse Events

Twenty-four patients reported a total of 112 treatment-emergent adverse events, with the majority of events of moderate intensity 53 (47%). The overall number of events and the intensity of these events are noted below (Table 5).

Three patients in the Immediate Group reported a total of four severe adverse events and two patients in the Delayed Group reported a total of four severe adverse events (Table 5). Severe injection site bruising (Patient B5) was considered by the Investigator to be related to study treatment. All of the remaining severe adverse events were not related.

Summary information on intensity of treatment-emergent adverse events is provided in Table 3.7 (Section 9). Individual adverse events are given in Listing 9.1 (Appendix C.1).

Table 5: Intensity of Adverse Events

Intensity of Events	Immediate Group 73 events*		Delayed Group 39 events*		Combined Groups 112 events*	
Overall (n, %)						
Mild	33	(45%)	16	(41%)	49	(44%)
Moderate	35	(48%)	18	(46%)	53	(47%)
Severe	4	(5%)	4	(10%)	8	(7%)

Severe Adverse Events**

System Organ Class MedDRA Term	Immediate Group N=15		Delayed Group N=14		Combined Groups N=29	
Gastrointestinal (n,%)						
Diarrhoea	1	(7%)	0		1	(3%)
Food poisoning	1	(7%)	0˙		1	(3%)
General & Administration Site (n,%)						
Injection site bruising	0		1	(7%)	1	(3%)
Infections & Infestations (n,%)						
Condyloma acuminatum	0		1	(7%)	1	(3%)
Postoperative infection	0		1	(7%)	1	(3%)
Urinary tract infection	1	(7%)	0		1	(3%)
Injury, Poisoning & Procedure (n,%)						
Sunburn	1	(7%)	0		1	(3%)
Surgical & Medical (n,%)						
Anal fistula excision	0		1	(7%)	1	(3%)

*Includes events with unknown intensity.
**Severe events listed only.
Source Data: Table 3.7, 30OCT03 – V_FINAL, AETAB4/V_TOTALAEINTEN/ 0_TOTALAES

Relationship of Adverse Events to Treatment

Nine (60%) patients in the Immediate Group and 8 (57%) in the Delayed Group experienced one or more treatment-related adverse events (Table 6). All of the treatment-related events were concerned with the skin and administration site, although there was one treatment-related episode of infection in the right cheek (Patient A9, Immediate Group) that occurred 2 weeks after the first injection. Treatment was delayed by 2 weeks but the infection resolved without antibiotic treatment.

The most common treatment-related adverse events were injection site bruising [11 (38%) patients] followed by skin nodules [9 (31%) patients], injection site discomfort [3 (10%) patients], injection site inflammation [3 (10% patients], and injection site erythema [3 (10%) patients].

One episode of treatment-related injection site bruising was severe (Patient B5, Delayed Group). The bruising occurred on the day of the first injection and resolved 6 days later. This patient did not experience any other severe adverse events and the second injection was associated with mild injection site bruising and discomfort.

There were 45 individual treatment related events noted in 17 patients. All events except for the nodules, induration and the infection in the right cheek were noted at the time of injection. The majority of events subsided within 4 days of occurrence. All events described as induration (1) and nodules (9) were noted in 10 patients at the Recall Visit. The patients did not know the dates of onset. The majority of nodules were noted as small lumps. No other data regarding these nodules were available.

Summary information on the relationship of treatment-emergent adverse events to study treatment is provided in Table 3.5 (Section 9). Individual adverse events are given in Listing 9.1 (Appendix C.1).

Table 6: Incidence of Treatment-Related Adverse Events

System Organ Class MedDRA Term	Immediate Group N=15		Delayed Group N=14		Combined Groups N=29	
Overall (n, %)	9	(60%)	8	(57%)	17	(59%)
General & Administration Site (n,%)						
Injection site bruising	7	(47%)	4	(29%)	11	(38%)
Injection site discomfort	2	(13%)	1	(7%)	3	(10%)
Injection site erythema	3	(20%)	0		3	(10%)
Injection site haemorrhage	0		1	(7%)	1	(3%)
Injection site induration	0		1	(7%)	1	(3%)
Injection site inflammation	0		3	(21%)	3	(10%)
Injection site nodule	6	(40%)	3	(21%)	9	(31%)
Injection site oedema	1	(7%)	1	(7%)	2	(7%)
Injection site tenderness	0		1	(7%)	1	(3%)
Infections & Infestations (n,%)						
Infection nos	1	(7%)	0		1	(3%)
Skin & Subcutaneous Tissue (n,%)						
Skin lesion nos	1	(7%)	0		1	(3%)

nos: not otherwise specified
Source Data: Table 3.5, 30OCT03 – V_FINAL, AETAB2/V_JUSTRELAT/ 0_JUSTRELAT

11-037

7.1.2 Unanticipated Adverse Device Effects (UADES)

No Unanticipated Adverse Device Effects were reported by any of the patients during the trial.

7.1.3 Serious Adverse Events

No serious adverse events were reported during the study (Table 3.6, Section 9).

7.1.4 Clinical Laboratory Assessments

Continuous Laboratory Parameters

There were no clinically or statistically significant differences between the groups in any laboratory values, in particular, lactate (Table 7). There were no discernible trends towards change from Baseline at Weeks 12 and 24, although there was a statistically significant change in bilirubin at Week 12 (Delayed Group) and in HDL cholesterol at Week 24 (Immediate Group). However, these changes were not clinically meaningful and are considered spurious findings. No changes in laboratory values were reported as adverse events.

More summary information on change from baseline in laboratory parameters is provided in Table 3.1 (Section 9). Full details for each patient are provided in Listing 5 (Appendix C.1).

11-038

Table 7: Clinical Laboratory Assessments - Change From Baseline

	Immediate Group		n	Delayed Group		n
ALT (U/l) (mean, SD)						
Week 12	-6.0	(15.7)	14	-5.3	(15.8)	12
Week 24	-1.8	(16.0)	14	-3.9	(20.1)	13
AST (U/l) (mean, SD)						
Week 12	-3.8	(9.3)	5	9.0		1
Week 24	1.0		1	N/A		0
Alkaline phosphatase (IU/l) (mean, SD)						
Week 12	-5.8	(13.6)	13	1.5	(18.0)	12
Week 24	-9.4	(14.0)	14	0.9	(25.6)	13
Bilirubin (mg/dl) (mean, SD)						
Week 12	2.3	(8.6)	12	-3.2	(4.4)*	11
Week 24	0.6	(9.2)	10	-2.3	(4.3)	12
CD4 (cells/mm^3) (mean, SD)						
Week 12	-70.0	(179.6)	14	-49.1	(146.9)	14
Week 24	-67.9	(137.9)	15	-14.4	(111.8)	14
Cholesterol HDL (mmol/l) (mean, SD)						
Week 12	-0.0	(0.2)	6	-0.1	(0.2)	9
Week 24	0.2	(0.2)*	7	0.1	(0.3)	9
Cholesterol LDL (mmol/l) (mean, SD)						
Week 12	-0.4	(0.5)	5	-0.0	(0.4)	5
Week 24	-0.1	(0.1)	4	0.0	(1.1)	5
Glucose (mmol/l) (mean, SD)						
Week 12	-0.9	(3.3)	13	-0.1	(1.6)	12
Week 24	-1.1	(3.8)	13	-0.3	(1.5)	14
Lactate (U/l) (mean, SD)						
Week 12	-0.3	(0.9)	9	0.0	(0.4)	9
Week 24	0.2	(1.5)	12	0.0	(0.4)	12
Total insulin (mU/l) (mean, SD)						
Week 12	5.6	(17.6)	3	0.1	(7.8)	4
Week 24	0.9	(16.0)	3	0.6	(15.8)	3
Triglycerides (mmol/l) (mean, SD)						
Week 12	-1.1	(4.6)	12	-0.3	(1.3)	12
Week 24	-1.5	(6.0)	15	-0.4	(1.9)	13

* p<0.05 by within-group paired t-test
Source Data: Table 3.1, 23OCT03 – V_FINAL, CHGLABS/V_TABLE3_1/ V_TABLE3_1

Viral Load

Although the viral load parameters between groups differed at baseline, there were no significant changes in viral load over time (Table 8).

More summary information on viral load is provided in Table 3.2 (Section 9). Full details for each patient are provided in Listing 5 (Appendix C.1).

Table 8: Viral Load

		Immediate Group N=15		Delayed Group N=14		p-value
Viral load (copies/ml) (n, %)						
Baseline	<50	7	(46.7)	13	(92.9)	0.007
	≥50	8	(53.3)	1	(7.1)	
Week 12	<50	8	(53.3)	12	(85.7)	0.060
	≥50	7	(46.7)	2	(14.3)	
Week 24	<50	8	(53.3)	13	(92.9)	0.017
	≥50	7	(46.7)	1	(7.1)	

Source Data: Table 3.2, 21OCT03 – FINAL, VIRAL_LOAD/VLCAT/0_VLCAT

7.1.5 Safety Summary

A total of 24 (83%) patients reported one or more treatment emergent adverse events. The most common adverse event was injection site bruising [11 (38%) patients] followed by skin nodules [9 (31%) patients].

Seventeen (59%) patients experienced one or more treatment-related adverse events. All episodes of injection site bruising and skin nodules were considered by the Investigator to be treatment-related. Other common treatment-related events were injection site discomfort [3 (10%) patients], injection site inflammation [3 (10%], and injection site erythema [3 (10%) patients].

One episode of treatment-related injection site bruising was severe. This was associated with the first injection and the patient did not experience further severe adverse events. All other treatment-related adverse events were mild or moderate. There were no serious adverse events.

There were no statistically significant or clinically meaningful differences between the groups or changes from baseline in any laboratory values, including CD4 cell counts and viral load.

11-040

7.2 EFFECTIVENESS

7.2.1 Acute Procedural Success

Dermal Thickness

Significant changes from Baseline in dermal thickness were recorded in the left and right naso labia and cheeks at Week 12 and 24 in the Immediate Group and at Week 24 only in the Delayed Group (Table 9). These data are also presented graphically in Figure 1, Panels 1 and 2.

Table 9: Dermal Thickness - Change From Baseline

Dermal Thickness (mm)	Immediate Group N=14 Weeks 12 and 24			Delayed Group N=8 Week 12, N=13 Week 24			
	Baseline Mean	Change from Baseline Mean (SD)	Within-Group p-value	Baseline Mean	Change from Baseline Mean (SD)	Within-Group p-value	Between-Group p-value
Treated areas							
Left Naso Labia							
Week 12	2.4	3.9 (2.1)	**<0.001**	2.4	0.1 (0.6)	0.774	**<0.001**
Week 24	2.5	5.3 (1.8)	**<0.001**	2.4	5.7 (2.1)	**<0.001**	0.525
Right Naso Labia							
Week 12	2.7	4.3 (2.9)	**<0.001**	2.3	0.2 (0.7)	0.448	**0.001**
Week 24	2.7	4.9 (2.3)	**<0.001**	2.5	6.0 (2.6)	**<0.001**	0.250
Left Cheek							
Week 12	2.4	4.1 (2.8)	**<0.001**	2.1	0.4 (0.4)	**0.037**	**0.001**
Week 24	2.5	4.9 (1.8)	**<0.001**	2.3	5.7 (1.8)	**<0.001**	0.247
Right Cheek							
Week 12	2.6	3.9 (2.4)	**<0.001**	2.3	0.3 (0.4)	0.121	**<0.001**
Week 24	2.6	4.9 (2.3)	**<0.001**	2.4	5.5 (2.3)	**<0.001**	0.487
Untreated areas							
Left Mouth							
Week 12	2.4	0.6 (1.2)	0.070	2.1	0.3 (0.5)	0.126	0.482
Week 24	2.5	-0.1 (1.2)	0.650	2.3	0.3 (0.8)	0.250	0.304
Right Mouth							
Week 12	2.5	0.6 (1.2)	0.094	2.4	0.1 (0.3)	0.593	0.250
Week 24	2.5	0.1 (0.9)	0.626	2.6	-0.0 (0.7)	0.968	0.688
Left Zygoma							
Week 12	2.4	0.1 (0.7)	0.529	2.0	0.2 (0.4)	0.128	0.706
Week 24	2.5	-0.2 (0.8)	0.307	2.2	0.1 (0.7)	0.775	0.337
Right Zygoma							
Week 12	2.6	0.1 (0.7)	0.499	2.4	0.4 (0.5)	0.090	0.438
Week 24	2.6	-0.1 (0.8)	0.475	2.4	-0.1 (0.4)	0.273	0.962

Significant values (p <0.05) are bolded.
Source Data: Table 2.1, 23OCT03 – V_FINAL, CHGULTRA/V_TABLE2_1/ V_TABLE2_1

11-041

In the treated areas (left and right naso labia and left and right cheeks) significant changes from baseline were measured 12 weeks after the initiation of treatment in both treatment groups i.e. at Week 12 in the Immediate Group and at Week 24 in the Delayed Group.

At Week 12, there was a significant difference between the Immediate and Delayed Groups in terms of skin thickness in the treated areas, as expected because this indicates that PLLA increased skin thickness in the treated facial areas. At Week 24, there was no difference between the groups, which shows that PLLA increased skin thickness in the Delayed Group and that the earlier increase in skin thickness in the Immediate Group was sustained at this time point.

There were no significant changes from Baseline or differences between the groups in the untreated areas of the mouth or zygoma either at Week 12 or at Week 24.

11-042

Figure 1: Change in Dermal Thickness by Ultrasound

Panel 1 Baseline to Week 12, Panel 2 Baseline to Week 24
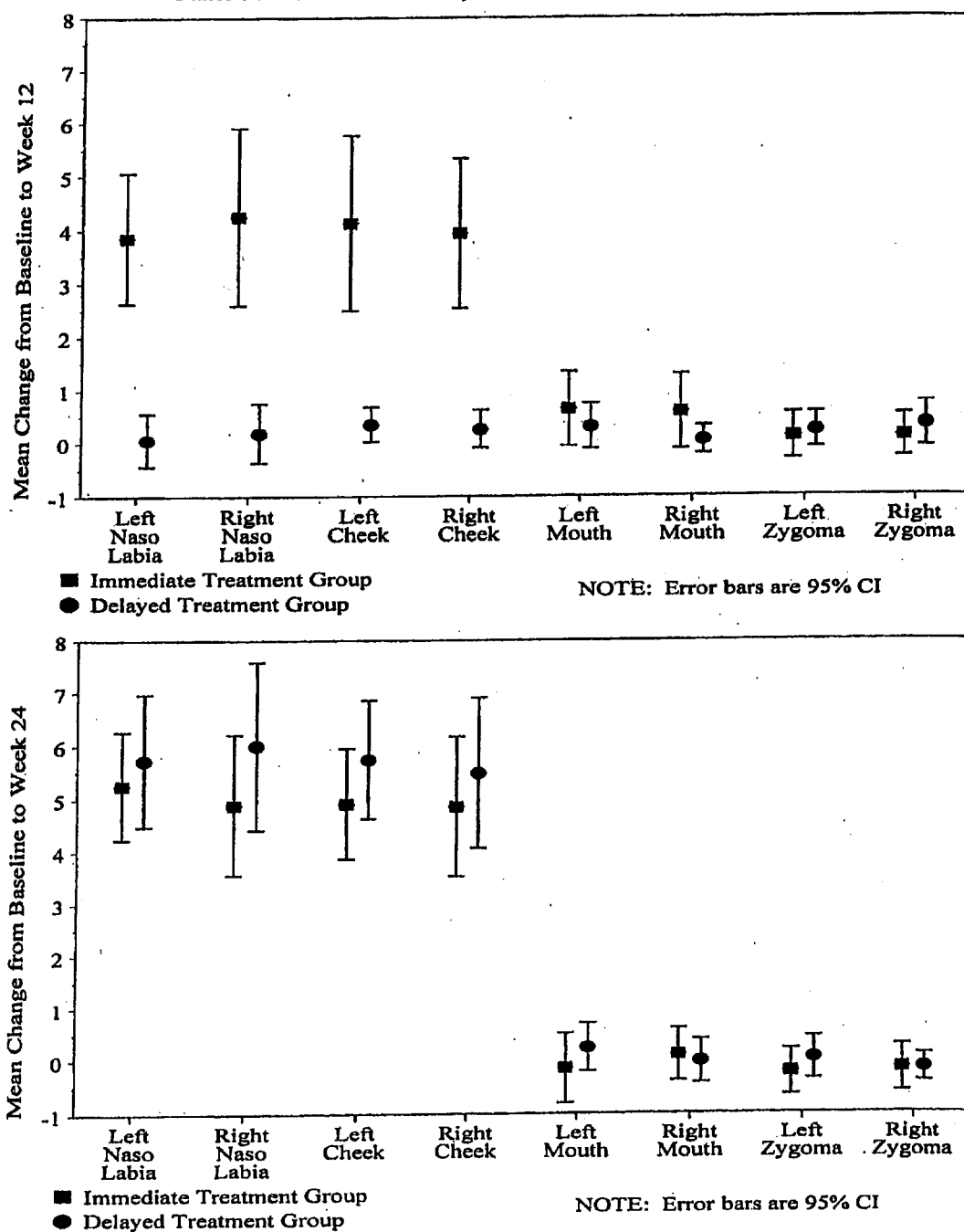
Source Data: Figure 1, 07NOV03, Figure_1.sas

11-043

More summary information on dermal thickness is provided in Table 2.1 (Section 9). Full details for each patient are provided in Listing 4 (Appendix C.1).

Visual Analogue Scale Scores

Significant improvements in perception of body part thinness, compared with Baseline, were recorded in the treated area of the face at Weeks 12 and 24 in the Immediate Group and at Week 24 in the Delayed Group (Table 10).

Table 10: Visual Analogue Scale Scores - Change From Baseline

| VAS Score (cm) | Immediate Group N=15 | | | Delayed Group N=14 | | | |
	Baseline Mean	Change from Baseline Mean (SD)	Within-Group p-value	Baseline Mean	Change from Baseline Mean (SD)	Within-Group p-value	Between-Group p-value
Treated area							
Face							
Week 12	2.3	4.9 (2.4)	<0.001	1.4	0.6 (1.7)	0.241	<0.001
Week 24	2.3	3.7 (1.9)	<0.001	1.4	4.5 (2.2)	<0.001	0.317
Untreated areas							
Arms							
Week 12	4.7	0.7 (2.6)	0.294	4.0	0.1 (2.5)	0.836	0.542
Week 24	4.7	0.3 (2.5)	0.609	4.0	0.6 (2.3)	0.372	0.791
Bottom							
Week 12	2.4	1.0 (2.2)	0.101	2.9	-0.3 (2.1)	0.612	0.116
Week 24	2.4	0.7 (2.4)	0.296	2.9	0.7 (1.5)	0.096	0.949
Legs							
Week 12	3.7	0.8 (2.1)	0.158	3.1	0.2 (2.2)	0.720	0.466
Week 24	3.7	0.4 (2.2)	0.486	3.1	1.1 (2.0)	**0.048**	0.342
Waist/abdomen							
Week 12	4.9	1.9 (3.4)	0.049	4.9	0.1 (4.3)	0.951	0.219
Week 24	4.9	1.6 (3.0)	0.056	4.9	0.4 (2.9)	0.593	0.295

Significant values (p <0.05) are bolded.
Source Data: Table 2.3, 29OCT03 – V_FINAL, CHGVAS/V_TABLE2_3/ V_TABLE2_3

VAS scores ranged between 0 (as thin as it has ever been) to 10 (not thin at all). As for skin thickness measured by ultrasound, significant changes from baseline were observed in the treated area of the face at 12 weeks after the initiation of treatment in both treatment groups i.e. at Week 12 in the Immediate Group and at Week 24 in the Delayed Group.

At Week 12, there was a significant difference between the Immediate and Delayed Groups in terms of perception of body part thinness in the treated areas, as expected because this indicates that the face had a "fuller" look. At Week 24, there was no difference between the groups, which shows that the perception of a "fuller" face occurred in the Delayed Group after treatment and that the earlier improvement in perception of thinness of the face in the Immediate Group was sustained at this time point.

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The mean direction of change in perception of body part thinness improved in the arms, bottom, legs and waist/abdomen in both groups and at both time points, but with the exception of waist/abdomen at Week 12 in the Immediate Group and legs at Week 24 in the Delayed Group, the differences were statistically significant. For the increase in waist/abdomen measurement, this could signify a progression of the underlying disease (lipodystrophy). As well, these areas were not treated with the product.

More summary information on VAS scores is provided in Table 2.3 (Section 9). Full details for each patient are provided in Listing 2 (Appendix C.1).

Anxiety and Depression Scores

Significant improvements in anxiety scores, compared with Baseline, were recorded at Weeks 12 and 24 in the Immediate Group (Table 11).

Table 11: HAD Scores - Change From Baseline

Score (units)	Immediate Group N=15			Delayed Group N=14 Week 12, N=14 Week 24			
	Baseline Mean	Change from Baseline Mean (SD)	Within-Group p-value	Baseline Mean	Change from Baseline Mean (SD)	Within-Group p-value	Between-Group p-value
Anxiety							
Week 12	8.7	-2.7 (4.6)	**0.041**	9.9	0.3 (4.0)	0.792	0.075
Week 24	8.7	-2.5 (3.6)	**0.016**	10.2	-2.5 (4.5)	0.072	0.963
Depression							
Week 12	6.0	-1.9 (3.4)	**0.047**	7.2	-0.2 (3.9)	0.841	0.218
Week 24	6.0	-2.1 (4.2)	0.070	7.2	-2.8 (4.2)	**0.029**	0.681

Significant values (p <0.05) are bolded.
Source Data: 2.2, 23OCT03 – V_FINAL, CHGANX/V_TABLE2_2/ V_TABLE2_2

Baseline mean HAD anxiety scores in both groups were within the range "suggestive of mood disorder". After 12 and 24 weeks, mean HAD anxiety scores in the Immediate Group had improved and were within the range of "normal". In the Delayed Group, HAD anxiety scores were within the range 8-10 at both post-treatment time points ("suggestive of mood disorder") although the treatment mean had improved at Week 24.

There was a significant difference between the Immediate and Delayed Groups at Week 12 but not at Week 24, indicating an effect of treatment in comparison with a control group.

Significant improvements in depression scores, compared with Baseline, were recorded at Week 12 but not at Week 24 in the Immediate Group. At Baseline, mean HAD depression scores were within, or close to, the range representing "normal" mood. Therefore, although improvements in treatment means occurred at Weeks 12 and 24 in the Immediate Group and at Week 24 only in the Delayed Group, the mean scores remained within the range representing "normal" mood.

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More summary information on HAD scores is provided in Table 2.2 (Section 9). Full details for each patient are provided in Listing 3 (Appendix C.1).

Facial Photography

As reported in a poster presented by ████████████████████████████ ▄▄▄▄▄▄▄▄ changes in photograph scores were observed in the treated (buccal) areas as well as the untreated temporalis area over 24 weeks. The greatest declines in severity scores were seen in the inferior area of the buccal fat pad. Scores in this area reduced from 15.3 at Baseline in the Immediate Group to 11.3 at Week 12, and 10.3 at Week 24. In the Delayed Group, scores in this area were 21 at Baseline, 20.3 at Week 12 and 14.3 at Week 24. Scores did not differ between groups at Baseline or at Week 24 but were lower at Week 12 in the Immediate Group. These data were not available for retrospective validation by the ████████████ on behalf of Dermik Laboratories.

7.2.2 Long-term Clinical Success

Approximately two years from the patient's baseline visit (i.e., 1 to 1.5 years after the completion of the study), patients were recalled for a follow up visit that was not part of original protocol. These data are presented below.

VAS at the Recall Visit

The improvement in the patients' perception of thinness in the face that was observed during the study was sustained at the Recall Visit assessment (Table 12). However, it should be noted that many of the patients commented that they had received additional treatments with PLLA between the end of the study and the Recall Visit.

More summary information on VAS scores at the Recall Visit is provided in Table 2.5 (Section 9). Full details for each patient are provided in Listing 11 and individual comments are transcribed in Listing 12 (Appendix C.1).

Table 12: Visual Analogue Scale Scores at the Recall Visit - Change From Baseline

	Immediate Group N=13	Delayed Group N=14
Arms (cm) (mean, SD)	1.2 (3.5)	1.4 (3.1)
Bottom (cm) (mean, SD)	1.3 (3.5)	0.8 (3.1)
Face (cm) (mean, SD)	3.3 (3.0) [a]	4.1 (2.0) [b]
Legs (cm) (mean, SD)	1.0 (3.7)	1.5 (2.7)
Waist/Abdomen (cm) (mean, SD)	2.2 (3.6) [c]	1.5 (3.5)

a: within-group $p<0.05$ by paired t-test
b: within-group $p<0.001$ by paired t-test
c: within-group $p=0.05$ by paired t-test.
Source Data: Table 2.5, 23OCT03 – V_FINAL, FOLLOWVAS/V_TABLE2_5/ V_TABLE2_5

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HAD at the Recall Visit

At the Recall Visit, the improvements in HAD anxiety and depression scores that were observed in the early phase of the study were sustained in the Delayed Group but less so in the Immediate Group (Table 13). However, as for VAS scores, many of the patients had additional treatments with PLLA between the end of the study and the Recall Visit.

More summary information on HAD scores at the Recall Visit is provided in Table 2.4 (Section 9). Full details for each patient are provided in Listing 10 and individual comments are presented in Listing 12 (Appendix C.1).

Table 13: HAD Scores at the Recall Visit - Change From Baseline

	Immediate Group N=13	Delayed Group N=13
Anxiety (mean, SD)	-0.8 (3.2)	-2.4 (4.1)
Depression (mean, SD)	-0.2 (2.8)	-3.5 (5.1) [a]

a: within-group p<0.05 by paired t-test.
Source Data: Table 2.4, 23OCT03 – V_FINAL, FOLLOWANX/V_TABLE2_4/ V_TABLE2_4

7.2.3 Effectiveness Summary

Significant changes from Baseline (p<0.001) in dermal thickness were observed in the areas treated with New-Fill (left and right naso labia and cheeks) at Week 12 and maintained through Week 24 in the Immediate treatment group. Significant changes from baseline were not observed until Week 24 (i.e., 12 weeks after initiation of treatment) in the Delayed Group (p<0.001), thus, the patients in the Delayed Group acted as a negative control to the Immediate treatment group at the Week 12 time point. A mean increase in dermal thickness of approximately 4-5 mm was observed twelve weeks after the initiation of treatment for both the Immediate Group (Week 12), and in the Delayed treatment group (Week 24). Areas that were not treated with the product failed to show improvements in dermal thickness at any time point and therefore acted as an internal control.

As expected, differences in dermal thickness at treated sites were significantly different between groups at Week 12 (p<0.001). No differences between groups in dermal thickness were observed at Week 24 of therapy, indicating that the treatment is effective regardless of initiating treatment immediately or delaying treatment.

Similar to the dermal thickness observations above, significant improvements in self-assessment visual analogue scores of the face were observed at Weeks 12 and 24 in the Immediate Group and at Week 24 in the Delayed Group.

Mean HAD anxiety scores were significantly improved in the Immediate Group at Weeks 12 and 24. At Baseline, mean HAD anxiety scores were within the range "suggestive of mood disorder" and the decreases in scores brought the patients' mean scores within the range of "normal". Mean HAD depression scores also showed improvements in the Immediate Group at Weeks 12 and 24 and at Week 24 in the Delayed Group.

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7.3   DISCUSSION

In HIV-related lipodystrophy, changes in fat deposition in the face are the most obvious and stigmatizing manifestation of the condition[4]. Plastic surgery, primarily autologous fat transfer, is the mainstay of treatment in acquired lipoatrophy. In patients with significant lipoatrophy, however, lack of a donor site can preclude autologous fat transfer. Additionally, transferred fat is likely to be subsequently lost in the on-going lipoatrophic process.

New-Fill[®] (PLLA) belongs to a group of new tissue augmentors, which is not only immunologically inert (i.e. it does not trigger inflammatory reaction), but which is also biodegradable and bioresorbable with total elimination of the substance and no residual active metabolite[5]. While PLLA is eliminated from the body as carbon dioxide by the lactate/pyruvate metabolism pathways, no discernible effect on plasma lactate is observed. Indeed, adverse systemic effects on all studied blood parameters, including CD4 cell count and viral load, were not observed in this study. PLLA has advantages over other facial implants in that it is hypoallergenic and biodegradeable, unlike silicon particles, which remain permanently resident in the skin and may trigger inflammatory reactions[6]. Additionally, the non-surgical administration technique enables individualization to suit the patient's facial contours, and leads to development of increased skin thickness but with retention of normal skin appearance and texture. The treatment does not address the underlying metabolic, lipoatrophic process. However, it does provide a treatment of the signs of lipoatrophy by augmenting skin thickness in the area of the lipoatrophic defect.

In the study reported here, treatment was limited to three injections per side. The injections were given into the deep dermis overlying the areas of facial lipoatrophy (buccal area), thereby leading to increases in dermal thickness and improvements in the contour deformity of the face.

The study was designed so that a treated cohort of patients (Immediate Group) could be compared with an untreated cohort (Delayed Group) at Week 12. This study design allowed for the ethical treatment of all patients who needed it, while allowing a comparison of treated and untreated patients after 12 weeks. At this time, the benefits of treatment were clearly evident by ultrasound. Furthermore, the patients' perception of thinness of the skin on the face was also significantly better in the treated group; anxiety scores were lower, as were depression scores.

Photographic assessments by the Investigators suggested that individuals did not always achieve 'normal' appearances at the treated sites suggesting further treatments may be required or that in some individuals the lipoatrophy was too profound to be disguised by expanding dermal thickness. Cohort evidence would suggest that individuals might continue to benefit from further injections, with some individuals having received 5 or more injections before achieving a satisfactory facial appearance[1]. Scores in the untreated areas assessed by photographs improved, possibly because the improved cheek appearance gives the assessor the impression of a generally 'fuller' face. However, it should be noted that there were no trends and no significant differences between the groups which, given the positive findings in the other assessments, suggests that this particular photographic rating system may not be reliable.

Although the effects of PLLA have been shown to persist beyond 2 years[7], its effects are not permanent and as such its aesthetic benefits may wane and will need to be repeated to suit the

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patient's needs. PLLA, however, does not restore lost fat mass at the site but rather expands dermal thickness, predominately through an increase initially in fibroblasts, and subsequently an increase in the deposition of collagen fibers[8]. This may have the advantage that as the underlying mechanism for the lipoatrophy is not clear and is likely to remain in progress in these individuals, the new tissue will not be then lost in the ongoing lipoatrophy. The disadvantage of PLLA treatment in this regard is that it is not *per se* a treatment for metabolic lipodystrophy and specifically does not address other body regions that may also be affected. PLLA is designed to address the signs of facial lipoatrophy.

The treatment was well tolerated and every patient who participated in the study completed the full treatment regimen of three injections. Twenty-four (83%) patients reported one or more adverse events. The most common adverse events were treatment-related and included injection site bruising [11 (38%) patients] and skin nodules [9 (31%) patients]. The treatment-related adverse events of bruising, discomfort, erythema, inflammation, haemorrhage, edema and tenderness were noted soon after injection and were transient in nature. Except for one episode of severe injection site bruising, most events were mild or moderate. Nodules and induration were reported at the Recall Visit and developed sometime after the initial study period (Week 24). The majority of nodules were noted as small lumps.

Overall, the risks of treatment were of minor, local, transient adverse events, and the benefits of the treatment were clear. Improvements in objective measures of skin thickness, self-assessments of facial thinness, and a reduction in anxiety and depression scores were demonstrated, indicating an acceptable risk-to-benefit ratio.

7.4 OVERALL CONCLUSIONS

- Treatment with a course of three injection sessions of New-Fill® (PLLA) was associated with a significant increase in skin thickness in the treatment area within 12 weeks of administration regardless of whether patients were treated immediately or if treatment was delayed by 12 weeks. This increase was still evident at 24 weeks after initiation of treatment in the Immediate Group.

- The treatment-related adverse events observed were consistent with the method of administration (dermal injections).

- Injections of New-Fill (PLLA) was found to be an efficacious and safe method of increasing facial thickness in HIV positive patients presenting with the signs of facial lipoatrophy.

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Title: A randomised open label study of Polylactic acid (New-Fill) injections for buccal fat pad wasting in persons with HIV related lipoatrophy   Final Protocol: 17 November 2000

Study Synopsis

Author: ███████████
Investigators: ████████████████████████████████ a
Site: ██████████
Financial Support: ████████████

Phase: Phase II, 2 arm study. 15 patients per arm, open label randomisation.

Statistics: No sample calculations used. All descriptive analyses against change from baseline values.

Patients: HIV positive. Moderate to severe buccal fat pad wasting requesting cosmetic management

Design: 2 arm study   a) Polylactic acid injections weeks 0, 2 and 4
b) Polylactic acid injections weeks 12, 14 and 16

Follow up: At baseline and week 2, 4, 6 and 12, 14, 16 and 24.
Fasting cholesterol, triglycerides, insulin, lactate,
CD4, VL, FBC, U&E, LFT.
Facial ultrasound at week 0, 12 and 24.
Patient and physician VA scale of severity of body shape change and questionnaire.
Adverse event reporting.

Outcomes:
Change in facial appearance as assessed by physician and patient
Buccal skin thickness by ultrasound at week 12 and 24
Change in VL and CD4 cell count,
Change in blood chemistry parameters
Adverse events.

Timelines: 3 months recruitment, 24 week follow-up.

Title: A randomised open label study of Polylactic acid (New-Fill) injections for buccal fat pad wasting in persons with HIV related lipoatrophy
Investigators: ███████████████████████████ a
Site: ███████████████████

Introduction:

The introduction of potent antiretroviral regimens (highly active antiretroviral therapy, HAART) has dramatically changed the natural history of HIV-1 infection. However, as these regimens do not eradicate HIV infection, therapy is currently considered life-long. Short-term, therapy with antiretrovirals has been associated with an increase in body weight and an improvement in nutritional status of HIV-1 infected patients. Longer-term (> 1 year) therapy has been associated with negative metabolic derangements and effects such as new-onset diabetes mellitus, hyperlipidaemia, and abnormal body fat distribution (also called lipodystrophy).

The pathogenesis of these metabolic and clinical phenomena remains speculative. No definitive management is established.

Reported clinical manifestations of lipodystrophy have not been homogeneous and range from central or localised adiposity to peripheral fat wasting. Patients with peripheral fat wasting frequently present with increased vein prominence as well as loss of facial fat pads such as the temporalis and naso-labial (also called Bichat's or buccal) fat pads. As the naso-labial fat pad lies in the communication triangle between the eyes and the mouth it is the most overtly stigmatising effect of lipodystrophy. The impact of loss of this fat pad is substantial, affecting social functioning, employment, sexual function and self esteem.

Polylactic acid injections (New Fill®) represent a new form of cosmetic 'filler' which provides for appearance improvement through both an initial bulk effect and subsequent stimulation of fibroblasts to increase collagen production. Anecdotal evidence form France suggests it may be beneficial in managing the loss of the naso-labial fat pad. No controlled study of new fill has been performed but it is approved by the Devices evaluation agency in the UK.

This study intends to evaluate the use of polylactic acid injections in an immediate versus delayed study design to enable assessment of both immediate (12 week) and prolonged (24 week) effects.

Financial Support: ███████████████████ t.

Sample size and statistics: 30 Patients total, 15 patients per arm, pilot study. Open label randomisation. No sample calculations used. All analyses descriptive against change from baseline values.

Inclusion Criteria:
HIV positive.
Physician and Patient agreed moderate to severe naso-labial fat pad loss
Willing and able to provide informed consent.
Not pregnant or lactating. Using adequate contraception as appropriate.

Exclusion Criteria:

Active Opportunistic disease or wasting syndrome
Planned plastic surgery
Current Growth hormone therapy
Oral hypoglycaemic therapy or lipid lowering agent commenced within one month
Current chemotherapy for malignancy.
Known polylactic acid hypersensitivity.

Design: 2 arm study with equal randomisation to
a) Polylactic acid injections weeks 0, 2 and 4
b) Polylactic acid injections weeks 12, 14 and 16
Randomisation will be by opening of sealed envelope on day 0.

Follow up:
At baseline and week 2, 4, 6 and 12, 14, 16 and 24.
Fasting cholesterol, triglycerides, insulin, lactate,
CD4, VL, FBC, U&E, LFT.
Facial ultrasound at week 0, 12 and 24.
Patient and physician VA scale of severity of body shape change and questionnaire.
Adverse event reporting.

Outcomes: Primary Endpoints: Change in facial appearance lipoatrophy grade as assessed by physician and patient
Buccal skin thickness by ultrasound at week 12 and 24
Change in VL and CD4 cell count,
Change in blood chemistry parameters
Adverse events.

Interim analysis for presentation when all patients completed 12 weeks.

Timelines: 3 months recruitment with 24 week follow-up.

Visit Flow Chart

	Screening	Baseline + week 2 and 4 (Arm A)	Week 12 + week 14 and 16 (Arm B)	Week 24
Injections				
Clinical	√	√	√	√
Lipids	√	√	√	√
U&E, LFT	√	√	√	√
Consent	√			
Lactate		√	√	√
Facial Ultrasound		√	√	√
VL, CD4		√	√	√
Questionnaire		√	√	√
Adverse Events		√	√	√
Photography	√	√	√	√

RREC 2600 – A randomised open label study of Polylactic acid (New-Fill) injections for buccal fat pad wasting in persons with HIV related lopoatrophy (Final Protocol version 1: 17 November 1999)

Design of the study:
Phase II, 2 arm, open label, randomised study

Sample size estimation
From the figures provided by Vexintrade, in a normal population, the thickness of dermis ranges from 1.1 mm to 4 mm.
The midpoint of these figures can be used to estimate the average thisckness of dermis in a **normal population: 2.6mm**

Mean thickness of dermis in normal population

Normal   Lipoatrophia

Normal value of dermis   **Abnormal** value
2.6 mm   1.3mm
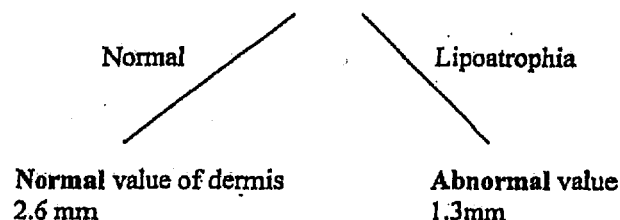
Assuming the distribution of dermis mesurements will be normally distributed. An increase in thickness of dermis mesurement by 50% from baseline is assumed to describe patients with success in treatment.

Thickness of dermis (mm)		Standard deviation of paired difference	Power	Significance level (2-sided)	Total no. of patients required
Lipoatrophia	Normal				
1.3	2.6	2.0	90%	5%	28
1.3	2.6	2.0	80%	5%	22

Assuming the thickness of dermis data will be normally distributed with pooled standard deviation of 2.0mm. To detect a difference of change in dermis by 50% from baseline with 90% certainty and 5% significance level the total sample required would be 30 subjects.
This is assuming the numbers of subjects recruited are unlikely to drop out after being recruited.

If the SD of the paired measurement is larger than what we have assumed (say 2.5) then the total sample required will need to be increased to total of 40 subjects for 90% power and 5% significance level.

Appendix A.1.2   Amendments to clinical study protocol

Ref: CH/LB/01.08

7 February 2003

Tel: ████████
Fax: ████████

RREC 2600: A randomised open label study of Polylactic acid (New-Fill) injections for buccal fat pad wasting in persons with HIV related lipoatrophy (Final Protocol version 1: 17 Nov 1999)

The above named study conducted at ████████ and completed around the end of last year was not officially closed as further administrative work was still being carried out. Since that time we have been approached by Dermik Laboratories, A Division of Aventis Pharma who have acquired the rights to the product, however, the study was sponsored through ████████ charity and therefore the data is owned by them..

Unfortunately no other study has been performed with this product (New-Fill) in HIV patients with lipoatrophy. Therefore, the company is interested in performing a full audit of our study potentially in preparation for a subsequent FDA audit for applications for marketing authorisation for New-Fill.

The ████████ have given consent for this to occur and ████████ (Chairman of the Trustees) and the company have signed the relevant confidentiality agreement.

In order for the company to look at the data, all the patients who took part in the study will need to sign a new consent form which explains why the company wish to access such information as in the original Patient Information Leaflet under the 'Confidentiality' section it only allowed doctors and nurses permission to view patient data. Therefore, please find enclosed a new Patient Information Leaflet & Consent form version 1: 31 Jan 03.

I hope you find the above satisfactory and that no ethical issues arise and look forward to receiving approval.

With best wishes

Yours sincerely

████████

Research Manager
HIV/GUM Directorate

Appendix A.1.3   Sample data collection form, EXCEL spreadsheet fields, HAD Scale I, and VAS

EXCEL DATA

HEADER	VARIABLES	LOCATION
Pt ID	Patient Initials	New-Fill data Spreadsheet
Gender	Gender	New-Fill data Spreadsheet
PI experience mts	Protease Inhibitor use	New-Fill data Spreadsheet
NRTI experience mts	Nucleoside Analogue use	New-Fill data Spreadsheet
Age	Patient age	New-Fill data Spreadsheet
DATA AT BASELINE, WEEKS 12 & 24		
BL CD4 / WK 12 CD4 / WK 24 CD4	CD4+ cell count	New-Fill data Spreadsheet
BL VL / WK 12 VL / WK 24 VL	Viral Load	New-Fill data Spreadsheet
BL TRI / WK 12 TRI / WK 24 TRI	Triglycerides	New-Fill data Spreadsheet
BL GLU / WK 12 GLU / WK 24 GLU	Glucose	New-Fill data Spreadsheet
BL CHOL HDL / WK 12 CHOL HDL / WK 24 CHOL HDL	Cholesterol HDL	New-Fill data Spreadsheet
BL CHOL LDL / WK 12 CHOL LDL / WK 24 CHOL LDL	Cholesterol LDL	New-Fill data Spreadsheet
BL LACTATE / WK 12 LACTATE / WK 24 LACTATE	Lactate	New-Fill data Spreadsheet
BL T INS / WK 12 T INS / WK 24 T INS	Total Insulin	New-Fill data Spreadsheet
BL ANX / WK 12 ANX / WK 24 ANX	Anxiety Score	New-Fill data Spreadsheet
BL DEP/ WK 12 DEP / WK 24 DEP	Depression Score	New-Fill data Spreadsheet
VAS SCORES:		
BL FACE / WK 12 FACE / WK 24 FACE	Face	New-Fill data Spreadsheet
BL ARMS / WK 12 ARMS / WK 24 ARMS	Arms	New-Fill data Spreadsheet
BL LEGS / WK 12 LEGS / WK 24 LEGS	Legs	New-Fill data Spreadsheet
BL BOT / WK 12 BOT / WK 24 BOT	Bottom	New-Fill data Spreadsheet
BL W/AB / WK 12 W/AB / WK 24 W/AB	Waist/Abdomen	New-Fill data Spreadsheet
ULTRASOUND DATA:		
DOI	Date of Inclusion	Ultrasound data Spreadsheet
Lt NL	Left Naso Labia	Ultrasound data Spreadsheet
Lt M	Left mouth	Ultrasound data Spreadsheet
Lt Z	Left Zygoma	Ultrasound data Spreadsheet
Lt C	Left Cheek	Ultrasound data Spreadsheet
Rt NL	Right Naso Labia	Ultrasound data Spreadsheet
Rt M	Right mouth	Ultrasound data Spreadsheet
Rt Z	Right Zygoma	Ultrasound data Spreadsheet
Rt C	Right Cheek	Ultrasound data Spreadsheet
ABBREVIATIONS:		
nd	not done	Either Spreadsheet
uns	unstable	Either Spreadsheet
nt	no result	Either Spreadsheet
md	missing data	Either Spreadsheet

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A RANDOMISED OPEN LABEL STUDY OF POLYLACTIC ACID (NEW-FILL) INJECTIONS FOR BUCCAL FAT PAD WASTING IN PERSONS WITH HIV RELATED LIPOATROPHY

DEMOGRAPHIC DATA

Patient Initials: _____   Arm: ☐ A (immediate)   ☐ B (delayed)

Date informed consent signed: _____ / _____ / _____

Patient year of birth: _____ or Age: _____   SEX: Male ☐   Female ☐

Race: Caucasian ☐   Hispanic ☐   Black ☐

          Asian ☐   Other ☐   Specify: _____

HIV + since: _____ give year   PI experience (months): _____

NRTI experience (months): _____

MEDICAL HISTORY

Please record below any medical condition that is currently ongoing for the patient.

CONDITION (print clearly) _____

CONDITION (print clearly) _____

CONDITION (print clearly) _____

CONDITION (print clearly) _____

ADDITIONAL LABORATORY DATA

Baseline	Week 12	Week 24
ALT _____	ALT _____	ALT _____
AST _____	AST _____	AST _____
Bilirubin _____	Bilirubin _____	Bilirubin _____
Alk Phos _____	Alk Phos _____	Alk Phos _____

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POLYLACTIC ACID (NEW-FILL) INJECTIONS

TREATMENT RECORD

Patient Initials: _____ | **SESSION # 1   DATE:** _____ / _____ / _____

DILUTION: _____ cc sterile water _____ cc anesthetic _____

LOT NUMBER: _____

AMOUNT OF PRODUCT INJECTED:

Right Cheek _____ cc / Left Cheek _____ cc

SESSION # 2   DATE: _____ / _____ / _____

DILUTION: _____ cc sterile water _____ cc anesthetic _____

AMOUNT OF PRODUCT INJECTED:

Right Cheek _____ cc / Left Cheek _____ cc

LOT NUMBER: _____

SESSION # 3   DATE: _____ / _____ / _____

DILUTION: _____ cc sterile water _____ cc anesthetic _____

AMOUNT OF PRODUCT INJECTED:

Right Cheek _____ cc / Left Cheek _____ cc

LOT NUMBER: _____

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ADDITIONAL INJECTIONS POST-STUDY

TREATMENT RECORD

Patient Initials: _____

DATE OF TREATMENT: _____ / _____ / _____

DILUTION: _____ cc sterile water _____ cc anesthetic _____

AMOUNT OF PRODUCT INJECTED:

Right Cheek _____ cc / Left Cheek _____ cc   Other area(s): _____ (cc)

Right Temple _____ cc / Left Temple _____ cc   Other area(s): _____ (cc)

LOT NUMBER: _____

DATE OF TREATMENT: _____ / _____ / _____

DILUTION: _____ cc sterile water _____ cc anesthetic _____

AMOUNT OF PRODUCT INJECTED:

Right Cheek _____ cc / Left Cheek _____ cc   Other area(s): _____ (cc)

Right Temple _____ cc / Left Temple _____ cc   Other area(s): _____ (cc)

LOT NUMBER: _____

DATE OF TREATMENT: _____ / _____ / _____

DILUTION: _____ cc sterile water _____ cc anesthetic _____

AMOUNT OF PRODUCT INJECTED:

Right Cheek _____ cc / Left Cheek _____ cc   Other area(s): _____ (cc)

Right Temple _____ cc / Left Temple _____ cc   Other area(s): _____ (cc)

LOT NUMBER: _____

11-165

FOLLOW-UP VISIT

Patient Initials: _____

Date of visit: _____ / _____ / _____

Date re-consent signed: _____ / _____ / _____

Follow-up Anxiety and Depression Score: ANX _____   DEP_____

Follow-up Visual Analog scale:

Face _____   Arms _____   Legs _____

Bottom _____   Waist / Abdomen _____

Ultrasound: Lt NL _____   Lt M _____   Lt Z _____   Lt C _____

Rt NL _____   Rt M _____   Rt Z _____   Rt C _____

Comments: _____

_____

_____

_____

ADVERSE EVENTS

Patient Initials: _____

Adverse Event	Start Date	Stop Date	Intensity	Related to product		Serious?	
				☐ Yes ☐ No		☐ Yes ☐ No	
				☐ Yes ☐ No		☐ Yes ☐ No	
				☐ Yes ☐ No		☐ Yes ☐ No	
				☐ Yes ☐ No		☐ Yes ☐ No	
				☐ Yes ☐ No		☐ Yes ☐ No	
				☐ Yes ☐ No		☐ Yes ☐ No	
				☐ Yes ☐ No		☐ Yes ☐ No	
				☐ Yes ☐ No		☐ Yes ☐ No	
				☐ Yes ☐ No		☐ Yes ☐ No	
				☐ Yes ☐ No		☐ Yes ☐ No	

11-167

CONCOMITANT MEDICATION

Patient Initials: _____

Drug	Daily Dose / Regimen	Start Date	Stop Date	Reason / Indication

HAD SCALE I

Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

Tick only one box in each section

I feel tense or 'wound up':   A   D

	A	D
most of the time	3	
a lot of the time	2	
occasionally	1	
Not at all	0	

I still enjoy the things I used to enjoy:

	A	D
Definitely as much		0
Not quite as much		1
Only a little		2
Hardly at all		3

I get a sort of frightened feeling as if something awful is going to happen:

	A	D
Very definitely and quite badly	3	
Yes, but not too badly	2	
A little but it doesn't worry me	1	
Not at all	0	

I can laugh and see the funny side of things:

	A	D
As much as I always could		0
Not quite as much now		1
Definitely not so much now		2
Not at all		3

Worrying thoughts go through my mind:

	A	D
A great deal of the time	3	
A lot of the time	2	
From time to time but not too often	1	
Only occasionally	0	

I feel cheerful:

	A	D
Not at all		3
Not often		2
Sometimes		1
Most of the time		0

I can sit at ease and feel relaxed:

	A	D
Definitely		0
Usually		1
Not often		2
Not at all		3

I feel as if I am slowed down: A   D

	A	D
Nearly all the time		3
Very often		2
Sometimes		1
Not at all		0

I get a sort of frightened feeling like 'butterflies' in the stomach:

	A	D
Not at all	0	
Occasionally	1	
Quite often	2	
Very often	3	

I have lost interest in my appearance:

	A	D
Definitely		3
I don't take as much care as I should		2
I may not take as much care		1
I take as much care as ever		0

I feel restless as if I have to be on the move:

	A	D
Very much indeed	3	
Quite a lot	2	
Not very much	1	
Not at all	0	

I look forward with enjoyment to things:

	A	D
As much as I ever did		0
Rather less than I used to		1
Definitely less than I used to		2
Hardly at all		3

I get sudden feelings of panic:

	A	D
Very often indeed	3	
Quite often	2	
Not very often	1	
Not at all	0	

I can enjoy a good book or television programme:

	A	D
Often		0
Sometimes		1
Not often		2
Very seldom		3

Please complete the following questions:

1   My face is:

as thin as it   not at all
has ever been   thin

|_____|_____|
0   1   2   3   4   5   6   7   8   9   10

2   My arms are:

as thin as it   not at all
has ever been   thin

|_____|_____|
0   1   2   3   4   5   6   7   8   9   10

3   My legs are:

as thin as it   not at all
has ever been   thin

|_____|_____|
0   1   2   3   4   5   6   7   8   9   10

4   My bottom is:

as thin as it   not at all
has ever been   thin

|_____|_____|
0   1   2   3   4   5   6   7   8   9   10

5   My waist/abdomen is:

as thin as it   not at all
has ever been   thin

|_____|_____|
0   1   2   3   4   5   6   7   8   9   10
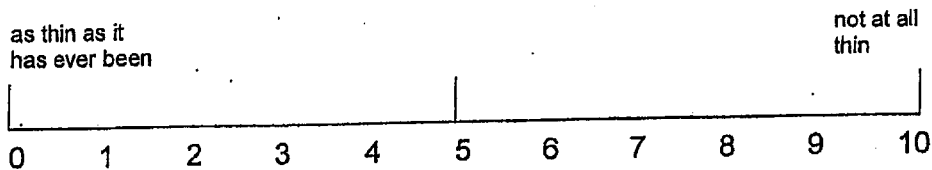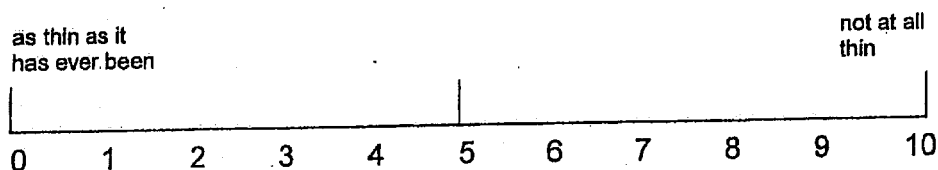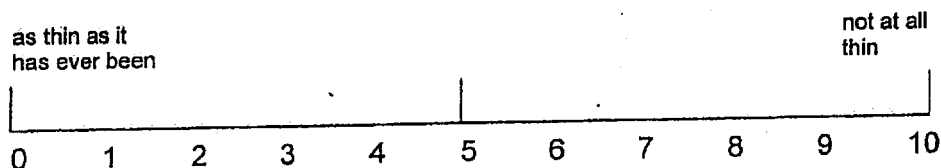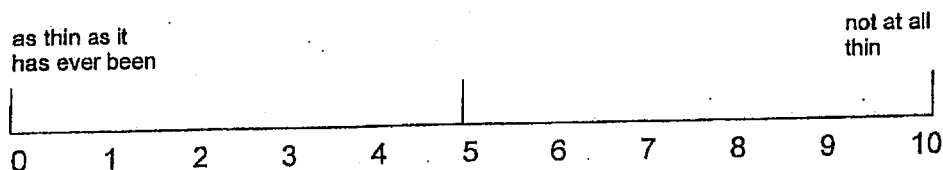
Interim Study Report

Study # APEX001

"Compassionate Use of Facial Intradermal Implants of New-Fill® in Persons with HIV-Associated Lipoatrophy of the Face"

Principal Investigator: ████████████████

Clinical Coordinator: ████████████████

Investigator Address: ████████████████████████████ach
████████████████
████████ ████████

Phone Number: ████████████

Fax Number: ████████████

Version Date: September 15, 2003

INVESTIGATOR STATEMENT:

To the best of my knowledge, the information contained in this interim report accurately reflects the subject status during the conduct of this compassionate use study.

████████████████   9/15/2003
████████████   Date

TABLE OF CONTENTS

1. INTRODUCTION

This report presents interim data from an ongoing clinical trial. This trial was conducted under the guidance of the FDA Office of Compliance and ███████████████████████ This interim report summarizes the data that has been collected as of August 19, 2003.

1.1 BACKGROUND

Lipoatrophy of the face has many known and many hypothesized mechanisms, including HIV disease, HIV antiretrovirals, and the aging process [1-5].

Multiple approaches have historically been used to correct these facial defects:

- Fat cell transplants by the Collman method have been used, but present technical difficulties with anesthetic and harvesting techniques. In addition the re-implantation tissue disappears at the same rate as the as the original loss through lipoatrophy.

- Non-biodegradable implants, the most common being silicone, present the disadvantage of possible immediate and delayed allergic responses and also the occurrence of inflammatory granulomas with possible rejection reactions[6].

- Other techniques use biodegradable implants. These are typically implants of animal origin, such as bovine collagen, which result in allergic reactions in 2-3% of all cases. These are re-absorbed particularly rapidly within a time span of several weeks to months[7-9]. Bovine collagen implants produce no permanent filling effect.

New-Fill® is a Poly-L-lactic acid water gel (PLLA), a synthetic polymer which is biodegradable and immunologically inert[10]. New-Fill® is well tolerated and effective in past research[11]. Other forms of PLLA have been used for many years in numerous therapeutic applications as resorbable suture material in ophthalmologic, neurological thoracic-abdominal surgery. Materials for osteosynthesis and ligament repair have been developed around the PLLA molecule.

PLLA, the substance in New-Fill®, is widely used in aesthetic procedures, such as the treatment of facial wrinkles. New-Fill® is a Class III device that has been approved by the French Notified Body G-Med (Groupement pour L' Evaluation des Dispositifs Medicaux – Department of Evaluation of Medical Devices)' on November 25, 1999 under the category "Wrinkles Filling Product." This product is commercially available worldwide in 27 countries including the European Union.

1.2 RATIONALE

The evaluation of New-Fill® to correct facial lipoatrophy defects in persons with HIV disease is already underway in several studies in Europe[11-15]. The results thus far are encouraging, and adverse events have been rare[11-15].

Additionally N ew-Fill h as a lso b een u sed i n t he U nited S tates b y s everal i ndividuals w ho h ad obtained the product through the DAAIR network[16] and through personal use importation protocols as allowed by U.S. Customs.

2. STUDY OBJECTIVES

Primary:

To evaluate the improvement of the facial defects seen in HIV-Associated Lipoatrophy after serial intradermal injections of New-Fill®.

Secondary:

- To evaluate the immediate and long term tolerability of New-Fill® intradermal injections.

- To evaluate the durability of the filling effect of New-Fill® intradermal injections.

- To evaluate the subjective psychological impact of facial defects associated with HIV lipoatrophy and any improvement in subjective psychological ratings as a result of treatment of these defects with New-Fill® intradermal injections.

3. ETHICS

This compassionate use study was conducted in compliance with the Institutional Review Board (IRB) and informed consent regulations set forth in the US Code of Federal Regulations (CFR) 21, Part 56, and in CFR 21, Part 50, respectively. The protocol was submitted to an independent IRB for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study and the consent procedure was made in writing to the investigator/sponsor before commencement of the study. The IRB consulted for this study was: ████████████████████████, ████████████████████, chairman ███████

This study was conducted using consent procedures as detailed by th████████

4. INVESTIGATORS AND ADMINISTRATIVE STRUCTURE

Principal Investigator and Sponsor, ████████████ conducted the study at ████████████. The ██████████████

Clinical Coordinator for the study ████████

5. INVESTIGATIONAL PLAN

5.1 OVERALL STUDY DESIGN

This report presents interim data (as of August 19, 2003) from an ongoing clinical trial.

This was an open label, uncontrolled, single center program. The goal of the study was to provide access to the product New-Fill® (Poly-L-lactic acid) for the treatment of HIV-associated lipoatrophy of the face.

Subjects received facial intradermal injections with New-Fill® every three to four weeks up to a maximum of six treatment sessions. Photographs were taken prior to the first treatment session and prior to each subsequent treatment session. In addition, each subject was photographed at six-month intervals until the end of the study period (two years). Self-evaluation questionnaires completed by the subject regarding treatment and tolerability were administered before the first treatment session, 3 weeks after the first treatment session, 6 weeks after the first treatment session, and 6 to 12 months after the final treatment session. A final questionnaire was administered at the end of the study period (two years).

5.1.1 Screening evaluations

The following evaluations occurred on Day 1:

- Clinical evaluation by ▬▬▬▬▬ History and limited physical exam)

- Consent Form explanation and witness consent.

- Facial Digital Photography

- Pretreatment questionnaire

5.1.2 Injections and monitoring

The following procedures were completed at the treatment sessions and/or follow-up visits:

- Each treatment was provided by ▬▬▬▬▬ using subdermal and subcutaneous bilateral injections at multiple sites with a total of 1 ml to 8 ml of New-Fill® in the treatment area. The volume of New-Fill injected at each treatment session was subjective and tailored to produce filling of desired facial defects.

- Treatment sessions were conducted at 3 to 4-week intervals, with a maximum variation of 10 days, to a maximum of 6 treatments in a single subject in the study period.

- Questionnaires were administered 3 weeks and 6 weeks after the first treatment session as well as 6 to 12 months after the last treatment session and at study completion. Refer to Table 5.1.

- Photography of treated areas was performed prior to each treatment session, and at 6-month intervals until the end of the study period (2 years).

TABLE 5.1: SUBJECT QUESTIONNAIRES

Question / Time point Assessed	Pre-treatment	3 weeks after first injection	6 weeks after first injection	6-12 months after last injection	Study completion (24 months or D/C)
How would you rate your self-esteem?	X		X	X	X
How do you feel your facial appearance effects you self-esteem?	X				
Rate your discomfort of the injection procedure		X			
How pleased are you at this time with the correction of your facial defect?		X			
How would you rate your overall correction in facial appearance since you received New-Fill?				X	X
List significant AEs		X	X	X	X

Table 5.2 – Flowchart of Study Procedures

Study Phase		Treatment Phase (3 to 4 week Intervals)				Follow Up Phase	
Procedures / Timepoint	Initial Treatment Visit	Week 3 (if needed)	Week 6 (if needed)	Week 9-15 (if needed)		Month 6 - 12	Month 24 or completion
Obtain Written Informed Consent	●						
Perform Physical Examination and Review Medical History	●						
Review of Prior and Concomitant Medications/Treatments	●	●	●	●		●	●
Review of Inclusion and Exclusion Criteria	●						
Treatment Procedure	●	●	●	●			
Adverse Event Assessment	●	●	●	●		●	●
Facial Photography	●	●	●	●		●	●
Self-Evaluation Questionnaire:							
How would you rate your self-esteem?	●		●			●	●
How would you rate your overall correction in facial appearance since you received New-Fill?						●	●
How do you feel your facial appearance affects your self-esteem?	●						
How pleased are you at this time with the correction of your facial defect?		●					

5.2 SELECTION OF STUDY POPULATION

All subjects enrolled were expected to have lipoatrophy of the face as a result of HIV and HIV antiretrovirals.

5.2.1 Inclusion Criteria

- Age > 18 years

- Facial defects demonstrable by digital photography

- Willingness to sign informed consent for treatment

- HIV seropositive

5.2.2 Exclusion Criteria

- Active infection of the face

- Non-compliance based on prior history

- Active cutaneous Karposi's Sarcoma of the face

- Facial injections of any product within the last 3 months

- Active Herpes Labialis

- Skin condition of the face that is incompatible with the study treatment

- Active treatment with interferon or systemic corticosteroids

- Pregnancy or breastfeeding

5.2.3 Removal of Subjects from Therapy or Assessments

Treatments were stopped in the case of local skin reactions, intolerance, or on the request of the study subject.

5.2.4 Prior and Concomitant Treatments

Subjects were excluded if they received facial injections of any product within the 3 months prior to study entry. Subjects were excluded if they received active treatment with interferon or systemic corticosteroids.

5.3 STUDY TREATMENT

5.3.1 Description

New-Fill® is a resorbable skin implant in the form of a sterile suspension, which is reconstituted from a dry powder by the addition of sterile water for injection (SWFI). This suspension contains microparticles of Poly-L-Lactic Acid. It is a synthetic polymer that is biodegradable, biocompatible and immunologically inert. New-Fill® is supplied in vials of lyophilized product. The contents of each vial are reconstituted with 3 ml of sterile water for injection (SWFI). At the request of the individual patient for anesthesia, 1 cc of 1% lidocaine was substituted for 1 cc sterile water to obtain a final volume of diluent of 3 cc total per vial.

5.3.2 Treatment Assignment Methods

This was an open-label study in which all eligible subjects are assigned to treatment with New-Fill®.

5.3.3 Treatment Compliance

██████████ administered treatments via subdermal and subcutaneous injection at 3 to 4-week intervals. Subjects received a minimum of one (1) and a maximum of six (6) treatment sessions, as determined by results and the agreement of the investigator and subject. All treatment sessions were recorded in the Treatment Record of the case report form (CRF), as well as standard patient records in the clinic.

5.4 STUDY ASSESSMENTS

5.4.1 Efficacy Assessment Methods

5.4.1.1 Investigator rating of Lipoatrophy

The investigator rated the degree of lipoatrophy of the cheeks and the temples of each subject using a scale of 1 to 5, with 1 = mild and 5 = most severe. Ratings were performed before treatment and one and 6 months after the final treatment. These ratings were recorded in the standard clinic chart, and were not revealed to the subject on the data Case Report Forms (CRFs).

5.4.1.2 Subject rating of Self Esteem

The subject rated their own self-esteem using a scale of 1 to 10, with 1 = very low and 10 = very high. Ratings were performed before treatment, 6 weeks after the first treatment, 6 to 12 months after the final treatment, and at study completion. Data was recorded on the Case Report Forms (CRFs) and was available to the investigator.

5.4.1.3 Subject Satisfaction of Correction of Facial Defects

The subject rated his satisfaction with treatment outcome on a scale of 1 to 10, where 1 = minimal correction and 10 = perfect correction. Ratings were performed 3 weeks, 6 to 12 months, and at study completion, and were recorded on the CRFs.

5.4.1.4 Photography

Each subject was photographed prior to the first treatment and prior to each subsequent treatment session. In addition, each subject was photographed at six-month intervals until study completion.

5.4.2 Safety Assessment Methods

5.4.2.1 Clinical Examination

A history and brief physical exam were performed at the baseline visit. Items noted in the subject medical records were: any active or inactive medical problems, surgical history, current medications, allergies, family history, tobacco and alcohol use, review of systems, social history and assessment of the visit including vital signs, weight and follow-up plan.

5.4.2.2 Adverse Events

Adverse events related to the treatments were collected on all subjects. Subjects were asked 3 weeks after the first injection to "Please list any significant adverse effects and their degree. Be specific, (i.e., bleeding from injections for 20 minutes, bruising at injection site for 3 days, etc.)" Subjects were asked 6 weeks after the last injection to "Please list any adverse effects of the procedure. Be specific". Subjects were also called at 6 to 12 months after the last treatment and asked to "Please list any significant long-term side effects of your treatments. Be specific". This same question was asked of each subject at study completion. Serious adverse events were reported immediately to the IRB, according to standard IRB protocols.

5.4.2.3 Injection Discomfort

Subjects were asked to rate the discomfort of the injection procedure 3 weeks after the first injection. The subjects rated the discomfort on a scale of 1 to 10, where 1 represented very little discomfort and 10 represented a very painful procedure.

5.5 CONCOMITANT MEDICATION

Collection of concomitant medications was noted for each subject at the baseline visit and recorded in the subject clinical medical record. Changes in subject medications were noted in the clinic medical record at the beginning of each treatment session.

5.6 TREATMENT COMPLIANCE

Subjects were scheduled to receive treatments at 3 to 4-week intervals. The majority of subjects were compliant with the visits, however 26 subjects were lost to follow-up after 1 or more treatment sessions. In addition, several subjects were unable to adhere to prescribed treatment intervals due to difficulty with travel and personal schedule conflicts (see Section 6.2).

6. STUDY POPULATION

6.1 DISPOSITION OF SUBJECTS

A total of 100 subjects were consented. The first subject was consented on 5/02/01 and the last subject was consented on 9/19/01. Since the study is currently ongoing, a breakdown of subject disposition is as follows:

- 4 subjects consented and failed to return for their first treatment visit, and were therefore not treated

- 96 subjects received at least one study treatment

  o 2 subjects expired during the study, one due to Cryptosporidiosis and one due to Mycobacterium Avium Complex (MAC)

  o 85 of 96 subjects completed 3 week follow up

  o 73 of 96 subjects completed 6 week follow up

  o 70 of 96 subjects completed 6 to 12 month follow up

  o 38 of 96 subjects have completed 24 month (completion) follow up

To date 24 subjects have been lost to follow-up and 32 subjects are in the ongoing/follow-up phase of the study.

6.2 PROTOCOL DEVIATIONS

A 6 to 12 month subject questionnaire was added when it was realized that the duration between the 6-week and the 24-month questionnaires was too lengthy.

As mentioned in Section 5.2, many subjects found it difficult to adhere to 3 to 4 week treatment intervals. The primary reason for this difficulty was proximity to the treatment location; many subjects reside█████████████████████and travel and scheduling conflicts often created treatment intervals of 4 to 6 weeks in these patients. This discrepancy in treatment intervals in commented upon in Section 10. Also, because of these difficulties, many subjects did not return in person for follow up visits, and many did not have follow up digital photography. In these

cases, subject questionnaires were completed via phone, fax, and e-mail, and some questionnaire intervals were missed.

6.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographics collected for this study included: sex, age, history, physical, vital signs, and concomitant medications.

- 100 male subjects consented (96 treated)

TABLE 6.1: DISTRIBUTION OF AGE AND RACE

Demographic Measures	N = 96
Age (years)	
Mean	44.5
Min, Max	32, 63
Race	N = 96
Caucasian	82
African-American/Hispanic	5
Hispanic	9
Number of years with HIV	N = 81
Mean	13.4
Min, Max	3, 23 (self-report)

7. EFFICACY RESULTS

7.1 OVERVIEW OF EFFICACY, PRIMARY PARAMETERS

Table 7.2 displays an overview of data collected regarding primary and secondary study parameters.

Subject satisfaction with the correction of cosmetic defects 6 to 12 months after treatment series was high, rating an average of 8.01 on a scale of 1 (minimal correction) to 10 (perfect correction). For those subjects who have completed the 24-month evaluation, the satisfaction rating remains high (7.52, N=38). The majority of subjects completing 24-month evaluations have had at least one additional treatment session to maintain cosmetic filling effect. At this time, the average time to re-treatment (with a single session to maintain cosmetic correction) appears to be near 12 months. Data are still pending overall on this measure. Whether this slowly diminishing cosmetic effect over time is due to collagen resorption, additional subcutaneous fat loss, or another process is beyond the scope of this compassionate use study.

Serial digital photography was used for subject reference only and has not been presented to a third party for analysis at this time, as additional consent procedures would be required.

Investigator rating of lipoatrophy improved significantly over the course of treatments. Using a scale of 1 to 5 (1 representing very mild facial fat loss and 5 representing very severe facial fat loss), the mean pre-treatment lipoatrophy rating was 3.2 (N=96) and the mean lipoatrophy rating at 6-12 months post-treatment was 1.36 (N=70).

7.2 PRIMARY AND SECONDARY PARAMETERS

Time point Assessed / Question	Pre-treatment	3 weeks after first injection	6 weeks after first injection	6-12 months after last injection	24 months after primary treatments
	N=96	N=85	N=73	N=70	N=38
How would you rate your self-esteem? (1 – 10)	6.32		7.94	8.01	8.0
How do you feel your facial appearance effects you self-esteem? (1 – 10)	8.07				
Rate your discomfort of the injection procedure (1 – 10)		3.54			
How pleased are you at this time with the correction of your facial defect? (1 – 10)		6.5			
How would you rate your overall correction in facial appearance since you received New-Fill?				8.0	7.52
Investigator Rating of Lipoatrophy (1 – 5)	3.2		1.37	1.36	

7.3 SECONDARY PARAMETERS

Subjects regarded their facial appearance as an important factor affecting their self-esteem. Self-esteem increased moderately over the course of their study treatments and remained stable through the follow up period thus far. Subject tolerance with treatment discomfort was acceptable, with the pain of procedure rated as an average of 3.54 on a scale of 1 (very little discomfort) to 10 (very painful).

As mentioned in section 7.1, the average time to re-treatment at this time appears to be near 12 months.

8. SAFETY

8.1 OVERVIEW OF SAFETY

In general New-Fill injections appear to be safe and well tolerated by the HIV population. Adverse events are as expected with an injectable cosmetic product and do not diminish subject satisfaction with the results.

8.2 EXTENT OF EXPOSURE

Of the 100 subjects who signed informed consent, 96 subjects received at least one treatment session. A total of 39 subjects received treatment of both the cheeks and temples, and 57 subjects received treatment of the cheeks alone.

Subjects could receive up to a maximum of 6 treatment sessions during the course of the study. Summaries of treatment sessions per subject are displayed in the following table.

TABLE 8.1 SUMMARY OF TREATMENT EXPOSURE

SESSION	# OF SUBJECTS
1 treatment	14
2 treatments	18
3 treatments	36
4 treatments	17
5 treatments	6
6 treatments	5
TOTAL	96

New-Fill was injected subdermally and subcutaneously in the described treatment areas. The volume of product injected per session was 2 to 8 cc (mean 6.2 cc). The number of treatment sessions performed per subject was 1 to 6 with a mean of 2.9 treatment sessions per subject.

8.3 ADVERSE EVENTS

8.3.1 Overview of Adverse Events

No serious adverse events related to study treatment have been reported during the trial. Injection related adverse events include: mild to moderate pain with injection, mild transient bruising, and formation of small, palpable, non-visible subcutaneous nodules. Incidence of these adverse events as reported by the subjects and the investigator are summarized in table 8.2.

TABLE 8.2   SUMMARY OF ADVERSE EVENTS

The following are newly reported adverse events over time

Adverse Events Reported by Subjects at 3 weeks (N=85)	Total Events
Mild pain at injection sites	17
Injection site bruising	9
Transient tingling at injection sites	1
Injection site nodule	6
Total at 3 weeks	33
Adverse Events Reported by Subjects at 6 weeks (N=73)	
Mild pain at injection sites	1
Injection site bruising	3
Transient tingling at injection sites	0
Injection site nodule	2
Total at 6 weeks	6
Adverse Events Reported by Subjects at 6 – 12 month (N=70)	
Mild pain at injection sites	0
Injection site bruising	0
Transient tingling at injection sites	0
Injection site nodule	11
Total at 6 – 12 months	11
Adverse Events Noted by Investigator at 6 – 12 months (N=70)	
Injection site nodule	39
Total at 6 – 12 months	39

Adverse events reported at 24 months have not been tabulated, but are similar to 6-12 month data.

8.4 DEATHS, DISCONTINUATIONS DUE TO ADVERSE EVENTS, AND OTHER SERIOUS ADVERSE EVENTS

8.4.1 Deaths

Two deaths have occurred during the study and neither was judged to be treatment-related. Two subjects expired after 2 or more treatment sessions, one due to Cryptosporidiosis and one due to MAC.

Subject 002D-R entered this study with a CD4 count of 3 and a past history of Kaposi's sarcoma and MAC. Four months after completion of treatment series, the subject developed night fevers and progressive, uncontrolled diarrhea. Clinical evaluation gave a diagnosis of Cryptosporidium enteritis, and the subject expired 4 months later, despite aggressive medical therapy.

Subject 062WLP entered the study with a CD4 count of less than 10 and a medical history of CMV retinitis, Pneumocystis Pneumonia, and severe wasting. Seven months after the completion of his treatment series, the subject experienced progressively worsening abdominal pain, night fevers, and anorexia, and was diagnosed with disseminated Mycobacterium Avium Complex, from which he eventually expired.

8.4.2 Discontinuations Due to Adverse Events

No subjects have discontinued the study due to an adverse event.

8.4.3 Other Serious Adverse Events

One subject suffered a cerebrovascular accident with residual neurologic deficit 8 months after completion of the treatment series. This CVA was judged as unrelated to study procedure by the primary care physician.

8.5 LABORATORY EVALUATION

Last available CD4 counts and HIV viral burden was noted in the clinic chart at the initiation of treatment. No other laboratory values were evaluated or followed during this compassionate use study.

8.6 CLINICAL EVALUATIONS

A history and brief physical exam were performed at the baseline visit. Items noted in the subject medical records were: any active and inactive medical problems, surgical history, current medications, allergies, family history, tobacco and alcohol use, review of systems, social history and assessment of the visit including vital signs, weight and follow-up plan.

9. CONCLUSIONS

Serial intradermal implants with New-Fill® are an effective, well tolerated, and long lasting method for the correction of facial defects associated with HIV lipoatrophy syndrome.

10. REMARKS

This study was designed to allow subjects access to this important new soft tissue filling product, New-Fill®, and to ascertain basic tolerability and safety of this product in the HIV population. Poor subject compliance with timing of treatments and poor availability of subjects for follow up photography limit the utility of this compassionate use study. The selection of "self-esteem" as a parameter for evaluation of psychological improvement in the subjects was probably a poor one, as many subjects were unable to characterize the psychological impact of their facial lipoatrophy in terms of "self-esteem".

Of note, however, is the large number of treatment session, which occurred without major product-related adverse events. The transient pain and bruising reported by some subjects was not any greater than that noted by other subjects receiving cosmetic injection procedures. The formation of palpable, but not visible subcutaneous nodules (approximately 1.0 to 2.0 mm) was noted by the investigator on greater than one-half of the subjects, but this nodule formation was often not noticed by the subjects, as evidenced by the lower rate of subject report for this phenomenon. This nodule formation has been noted by other researchers in earlier work with this product, and has not been a hindrance to the further use of this product.

This compassionate use study does not examine the mechanism for the slowly waning cosmetic effect observed in HIV lipoatrophy patients. Presumably, some of this loss of effect is due to continued subcutaneous fat loss, while some is due to other factors.

The scale used by the investigator to rate facial lipoatrophy was not standardized. Subjects did not rate their lipoatrophy before and after treatment using the same scale, but rather rated their satisfaction with the improvement of their facial appearance overall. Standardized lipoatrophy rating systems would be useful for future investigations dealing with HIV-associated lipoatrophy.

Due to the variation in timing of treatment visits, it is impossible to determine the ideal treatment interval for this product based upon this study alone. However, many subjects noted continued improvement in facial appearance after 4 weeks, leading the investigator to believe that treatment intervals of greater than 4 weeks may be acceptable or ideal. Further investigation is warranted to determine if there exists and ideal "window" for timing of treatment intervals.

COMPASSIONATE USE OF FACIAL INTRADERMAL IMPLANTS OF NEW-FILL® IN PERSONS WITH HIV-ASSOCIATED LIPOATROPHY OF THE FACE

AN OPEN LABEL, SINGLE SITE STUDY

Protocol Number 001
Version 18 April 2001

Principal Investigator

██████████████
████████████████

Clinical Coordinator

████████████████

CONTENTS

STUDY SUMMARY

The goal of this study is to provide access to the product New-Fill® (polyactic acid, poly-L-lactic acid) for the treatment of HIV-associated lipoatrophy of the face.

All patients enrolled are expected to have lipoatrophy of the face as a result of HIV and HIV antiretrovirals.

1 – OBJECTIVES

1.1 Primary Objective
To evaluate the improvement of facial defects after serial intradermal injections of New- Fill®.

1.2 Secondary Objectives
-To evaluate the immediate and long term tolerability of New- Fill® intradermal injections.
-To evaluate the durability of the filling effect of New Fill intradermal injections.

2 - METHODOLOGY

This is an open label, uncontrolled, single center program. The duration of follow up with each patient will be two years.

3 – ELIGIBILITY CRITERIA

3.1 Inclusion Criteria
-Age > 18 years
-Facial defect demonstrable by digital photography
-Willingness to sign informed consent for treatment
-HIV seropositivity

3.2 Exclusion Criteria
-Active infection of the face
-Non-compliance based on prior history
-Active cutaneous Kaposi's Sarcoma of the face
-Facial Injections of any product within the last 3 months
-Active Herpes Labialis
-Skin condition of the face that is incompatible with the study treatment
-Active treatment with interferon or systemic corticosteroids
-Pregnancy or breastfeeding

13-025

4 – STUDY SCHEMA

Patient presents with demonstrable facial defect desiring correction.

Intradermal New- Fill® Injections: The patient will receive facial intradermal injections with New Fill, using 1 ml to 6 ml of New- Fill® (0.15 g polyactic acid per 3 ml) per session. Sessions will be 3 weeks apart. Patients will receive a minimum of one(1) and a maximum of six(6) treatment sessions, as determined by results and the agreement of the investigator and subject.

Serial Digital Photography: Each subject will be photographed prior to the first treatment session and prior to each subsequent treatment session. In addition, each subject will be photographed at six month intervals until the end of the study period (two years).

Self-Evaluation Questionnaire: Each subject will complete a questionnaire regarding treatment and tolerability before the first treatment session and after the second treatment session. A final questionnaire will be administered at the end of the study period (two years).

5 – STUDY ENDPOINTS

5.1 Primary Endpoint
Evaluation of the percentage of patients who have responded satisfactorily as self-reported and recorded by serial photography.

5.2 Secondary Endpoints
-Summarize demonstrable effect of intradermal injections over 2 year study period
-Summarize tolerability of injections by subject self-report
-Summarize adverse events

6 – DURATION OF STUDY

24 months (2 years)

7 – SAMPLE SIZE

The study will be closed to accrual when sample size reaches 100 subjects.

8 – START OF STUDY

April 2001

9 - INTRODUCTION AND RATIONALE

Lipoatrophy of the face has many known and many hypothesized mechanisms, including HIV disease, HIV antiretrovirals, and the aging process itself (1,2,3,4,5).

Multiple approaches have historically been used to correct these facial defects:

-Fat cell transplants by the Collman method have been used, but present technical difficulties with anesthetic and harvesting techniques. In addition the re-implanted tissue disappears at the same rate as the original loss through lipoatrophy.

-Non-biodegradable synthetic implants, the most common being silicone, present the disadvantage of possible immediate and delayed allergic responses and also the occurrence of inflammatory granulomas with possible rejection reactions (6).

-Other techniques use biodegradable implants. These are typically implants of animal origin, such as bovine collagen, which result in allergic reactions in 2-3% of all cases. These are re-absorbed particularly rapidly within a time span of several weeks to months (7,8,9).

New Fill® is a polyactic acid water gel (PLA), a synthetic polymer which is biodegradable, biocompatible and immunologically inert (10). New Fill is well tolerated and effective in past research (11). PLA has been used for many years in numerous therapeutic applications as resorbable suture material in ophthalmologic, neurologic, and thoraco-abdominal surgery. Materials for osteosynthesis and ligament repair have been developed around the PLA molecule.

PLA, the substance in New-Fill®, is widely used in aesthetic procedures, such as the treatment of facial wrinkles. New-Fill® has been approved by the French regulatory authorities since November 1999.

The evaluation of New Fill to correct deep facial effects is already underway in an international, multicenter study. Results thus far are encouraging, and adverse events have been rare.

10 – SUBJECT SCREENING

Screening evaluations will occur on Day 1, and will comprise

-Clinical evaluation by Principal Investigator, History and Limited Physical
-Consent Form explanation and witnessed consent
-Facial Digital Photography
-Pretreatment questionnaire

11 – TREATMENT AND MONITORING

Injections and monitoring:
-Each injection visit will be provided by the Principal Investigator: injection at multiple sites with 1 ml to 6 ml of New-Fill® in the middle layers of skin in the treatment area. Volume of New-Fill® injected at each treatment will be subjective and tailored to produce filling of desired facial defects.
-Bilateral injections will be given at 3 week intervals, with a maximum variation of 10 days, to a maximum of 6 treatments in a single subject in the study period.

5

Treatment will be stopped in the case of local skin reactions, intolerance, or on request of the study subject.

A 3 week questionnaire will be administered before the second treatment session. A 6 week questionnaire will be administered prior to the third injection, or six weeks after the first injection if only two injection sessions are needed by a subject. A final questionnaire will be administered at study completion.

Photography of treated areas will be performed prior to each treatment session, and at 6 month intervals until the end of the study period (2 years).

12 – ETHICAL CONSIDERATIONS

11.1 Data Collection
Monitoring will be performed by the Principal Investigator and the Clinical Coordinator at the designated study site.

11.2 Study Site
The only designated study site will be ████████████████████

11.3 Confidentiality
The case record forms and study medication will be stored in a locked place, accessible only the persons involved in the conduct of the study.

11.4 Regulatory Issues
The study will be conducted using consent procedures as detailed by the ████ Investigational Review Board.

11.5 Emergency Medical Services
A physician licensed to practice medicine in th████████████ will be on call and available 24 hours per day for study participants. ████████████████ a major medical center, is located 0.5 miles from the study center and is available 24 hours per day for emergency services.

13 – DATA COLLECTION

At the completion of the study, data reported by patient questionnaires will be tabulated and summarized by the study personnel. Photographic images of subject progression will be made available to interested parties, provided adequate subject consent has been obtained for their distribution.

14 – REFERENCES

1. Carr A, Samaras K, Chisholm J, Cooper DA. *Pathogenesis of HIV-1 protease inhibitor-associated peripheral lipodystrophy, hyperlipidemia, and insulin resistance.* Lancet 1998, 351 : 1881-3.
2. Gervasoni C, Ridolfo AL, Trifiro G, et al. *Redistribution of body fat in HIV-infected women undergoing antiretroviral therapy.* AIDS 1999, 13 : 485-471.
3. Saves M, Raffi F, Capeau J, Lang JM, Peyromond D, Basdevant A, Roloff S, Chene, G, and the APROCO Study Group. *Factors related to the presence of fat redistribution in HIV-infected patients treated with protease inhibitor containing regimens – APROCO Cohort.* 7th Conference of Retrovirus and Opportunistic Infections, San Francisco, January 30 – February 2, 2000.

4. Boufassa F, Dulioust A et al. *Lipodystrophy and metabolic disorders in 646 HIV-1 infected patients previously treated with or without protease inhibitors.* 7th Conference on Retrovirus and Opportunistic Infections.
5. Miller JE, Emery S, et al. *The Australian prevalence survey of lipodystrophy syndrome.* 7th Conference on Retrovirus and Opportunistic Infections.
6. Faure M. *Complications des implants de silicone et autres materiaux dits inertes.* Ann. Dermatol. Venerol. 1995, 122 : 455-459.
7. Stegman SJ, Chu S, et al. *A light and electron microscopic evaluation of Zyderm collagen and Zyplast collagen implants in aging human facial skin.* Arch. Dermatol. 1997, 123 : 1644-1649.
8. Pons-Guiraud A. *Reactions of delayed hypersensitivity with implants of bovine collagen. A study of 810 patients.* Nouv. Dermatol. 1992, 11 : 422-432.
9. Ghersetich I, Teofoli P, et al. *Ultrastructural study of hyaluronic acid before and after the use of pulsed electromagnetic field, electrorydesis, in the treatment of wrinkles.* Int. J Dermatol. 1984, 33 : 661-663.
10. Chadrashekar G, Udupa N, et al. *Biodegradable injectable implant systems for long- term drug delivery using ply (lactic-co-glycolic) acid copolymers.* J. Pharm. Pharmaco. 1996, 48 : 669-674.
11. Amard P, Saint-Marc T, Katz P. *The effects of polyactic acid (New Fill®) as therapy for lipoatrophy of the face.* 2nd International Workshop of Adverse Drug Reactions ad Lipodystrophy in HIV, Toronto, Canada, 13,14,15 September 2000.

15 – STUDY MEDICATION

New-Fill® will be purchased for the study by the Principal Investigator from the Manufacturer. The address of the manufacturer is: Biotech Industry, S.A., 21 Rue Bernard HAAL, L 1711 Luxembourg, telephone 00 352 26 25 94 62. The principal Scientific Director of Biotech Industry, A.S., is ███████ a Doctor of Pharmacy.

A New-Fill® product manuscript accompanies this protocol.

Compassionate Use of Facial Intradermal Implants of New-Fill® in Persons
with HIV-Associated Lipoatrophy of the Face

Protocol 001   Version 18 April 2001

PRE-TREATMENT QUESTIONNAIRE

Subject Code: _____   Date: _____

1) What is the primary facial defect you are desiring to treat?

___ Wasting of the cheeks   ___ Wasting of the temples

2) On a scale of 1 to 10, how would you rate your self esteem? 1 represents very low, 10 very high.

___ (1 to 10)

3) On a scale of 1 to 10, how do you feel your facial appearance effects your self esteem? 1
represents very little, 10 very much.

___ (1 to 10)

Compassionate Use of Facial Intradermal Implants of New-Fill® in Persons
with HIV-Associated Lipoatrophy of the Face

Protocol 001   Version 18 April 2001

THREE WEEKS AFTER FIRST INJECTION

Subject Code: _____   Date: _____

1) On a scale of 1 to 10, please rate the discomfort of the injection procedure. 1 represents very little discomfort, 10 very painful.

   __ (1 to 10)

2) On a scale of 1 to 10, how pleased are you at this time with the correction of your facial defect? 1 represents not pleased, 10 very pleased.

   __ (1 to 10)

3) Please list any significant adverse affects and their degree. Be specific. (ie, bleeding from injections for 20 minutes, bruising at injection sites for 3 days, etc.)

9   13-031

Compassionate Use of Facial Intradermal Implants of New-Fill® in Persons
with HIV-Associated Lipoatrophy of the Face

Protocol 001   Version 18 April 2001

<u>SIX WEEKS AFTER FIRST INJECTION</u>

Subject Code: _____   Date: _____

1) On a scale of 1 to 10, how do you rate your self-esteem at this time, after 2 treatments with New Fill®? 1 represents very low, 10 very high.

___ (1 to 10)

2) Please list any adverse effects of the procedure. Be specific.

Compassionate Use of Facial Intradermal Implants of New-Fill® in Persons
with HIV-Associated Lipoatrophy of the Face

Protocol 001   Version 18 April 2001

STUDY COMPLETION QUESTIONNAIRE

Subject Code: _____   Date: _____

1) On a scale of 1 to 10, how would you rate your overall correction in facial appearance since you received New Fill®? 1 represents minimal correction, 10 represents perfect correction.

___ (1 to 10)

2) Please list any significant long-term side effects of your treatments. Be specific.

3) On a scale of 1 to 10, how would you rate your self-esteem after New Fill® treatments? 1 represents very low, 10 represents very high.

___ (1 to 10)

13-033

Compassionate Use of New-Fill®
Apex Protocol #001

Treatment Record

Subject Code: _____

Date	Site(s) Injected	Total cc's New-Fill	Comment

13-034

Interim Study Report

████████████

"Use of Intradermal Implants of New-Fill® in Persons with HIV-Associated Lipoatrophy of the Face"

Principal Investigator: ████████████

Clinical Coordinator: ████████████

Investigator Address: ████████████████████████h
████████████
████████████

Phone Number: ████████████
Fax Number: ████████████

Version Date: September 23, 2003

INVESTIGATOR STATEMENT:

To the best of my knowledge, the information contained in this interim report accurately reflects the subject status during the conduct of this clinical study.

████████████   9/25/2003

                                       Date

TABLE OF CONTENTS

1. INTRODUCTION

This report presents interim data from an ongoing clinical trial. This trial was conducted under an Investigator Initiated Treatment IDE (████████████). This interim report summarizes the data that has been collected as of Sept 18, 2003.

1.1 BACKGROUND

Lipoatrophy of the face has many known and many hypothesized mechanisms, including HIV disease, HIV antiretrovirals, and the aging process [1-5].

Multiple approaches have historically been used to correct these facial defects:

- Fat cell transplants by the Collman method have been used, but present technical difficulties with anesthetic and harvesting techniques. In addition the re-implantation tissue disappears at the same rate as the as the original loss through lipoatrophy.

- Non-biodegradable implants, the most common being silicone, present the disadvantage of possible immediate and delayed allergic responses and also the occurrence of inflammatory granulomas with possible rejection reactions [6].

- Other techniques use biodegradable implants. These are typically implants of animal origin, such as bovine collagen, which result in allergic reactions in 2-3% of all cases. These are re-absorbed particularly rapidly within a time span of several weeks to months [7-9]. Bovine collagen implants produce no permanent filling effect.

New-Fill® is a Poly-L-lactic acid water gel (PLLA), a synthetic polymer which is biodegradable and immunologically inert [10]. New-Fill is well tolerated and effective in past research [11]. Other forms of PLA have been used for many years in numerous therapeutic applications as resorbable suture material in ophthalmologic, neurological thoracic-abdominal surgery. Materials for osteosynthesis and ligament repair have been developed around the PLA molecule.

PLLA, the substance in New-Fill, is widely used in aesthetic procedures, such as the treatment of facial wrinkles. New-Fill is a Class III device that has been approved by the French Notified Body G-Med (Groupement pour L' Evaluation des Dispositifs Medicaux – Department of Evaluation of Medical Devices)' on November 25, 1999 under the category "Wrinkles Filling Product." This product is commercially available worldwide in 27 countries including the European Union.

1.2 RATIONALE

The evaluation of New-Fill® to correct facial lipoatrophy defects in persons with HIV disease is already underway in several studies in Europe [11-15]. The results thus far are encouraging, and

adverse events have bee rare[11-15]. This investigator has also fully accrued subjects for a limited study of New-Fill® in this same population[16]. Results to date are very positive, and no serious adverse events related to New-Fill® have been reported to this investigator.

Additionally New-Fill® has also been used in the United States by several individuals who had obtained the product through the DAAIR network[17].

2. STUDY OBJECTIVES

Primary:

To evaluate the improvement of facial defects after serial intradermal injections of New-Fill®.

Secondary:

- To evaluate the immediate and long term tolerability of New-Fill® intradermal injections.

- To evaluate the durability of the filling effect of New-Fill® intradermal injections.

- To evaluate the safety of New-Fill® intradermal implants in the setting of HIV-associated lipoatrophy of the face.

3. ETHICS

The present study was conducted in compliance with the Institutional Review Board (IRB) and informed consent regulations set forth in the US Code of Federal Regulations (CFR) 21, Part 56, and in CFR 21, Part 50, respectively. The protocol was submitted to an independent IRB for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study was made in writing to the investigator/sponsor before commencement of the study. The IRB consulted for this study was: ██████████████████████
████████; chairman ███████████████████████

Informed Consent procedures were performed in accordance with the procedures of ███████

This study was conducted according to the International Conference on Harmonization (ICH) standards of Good Clinical Practice (GCP) guidelines and in agreement with the latest revision of the Declaration of Helsinki as well as applicable local regulations.

4. INVESTIGATORS AND ADMINISTRATIVE STRUCTURE

Principal Investigator and sponsor ██████████████ s conducting the study at ████
██████ The Clinical Coordinator for the study is ███████████

██████████ CONFIDENTIAL

13-051

5. INVESTIGATIONAL PLAN

This report presents interim data (as of September 18, 2003) from an ongoing clinical trial.

5.1 OVERALL STUDY DESIGN

This is an open label, uncontrolled, single center program. The goal of the study is to assess the efficacy and safety of New-Fill® (Polylactic acid) for the cosmetic treatment of HIV-associated lipoatrophy of the face.

Subjects receive facial intradermal injections with New-Fill® every four weeks up to a maximum of six treatment sessions. Photographs are taken prior to the first treatment session, before each treatment session, at 6 and 12 months after the final treatment session, and in the event of an adverse reaction. Self-evaluation questionnaires completed by the subject regarding treatment and tolerability are administered before and immediately after the first treatment session, before each treatment session, and at the final treatment session. A questionnaire is also administered at 6 and 12 months after the final treatment session. The investigator completes evaluations before the first treatment session, before the final treatment session, and at 6 and 12 months after the final treatment session.

5.1.1 Screening evaluations

The following evaluations occurred on Day 1:

- Clinical evaluation by ███████ (History and limited physical exam)

- Laboratory evaluation of serum chemistries, including liver function tests (LFTs), serum bicarbonate levels, and in the case of decreased serum bicarbonate or positive anion gap, serum lactate levels to determine if lactic acidosis in present.

- Consent Form explanation and witness consent.

- Facial Digital Photography

- Pretreatment questionnaire

- Pre-menopausal female study subjects had serum pregnancy testing prior to New-Fill injections to exclude pregnancy. Last menstrual period is recorded in the subject record. Methods of birth control are discussed with the subject, and the chosen method of reliable birth control is recorded in the subject record. The importance of not becoming pregnant during the study was emphasized to the subject.

5.1.2 Injections and monitoring

The following procedures were completed at the treatment sessions and/or follow-up visits:

- Each treatment was provided by ████████ injections at multiple sites with a total of 1 ml to 9 ml of New-Fill® subcutaneously and subdermally in the treatment area. The volume of New-Fill® injected at each treatment session was subjective and tailored to produce filling of desired facial defects.

- Treatment sessions were given at 4 to 6-week intervals, with a maximum variation of 10 days, to a maximum of 6 treatments in a single subject in the study period.

- A subject questionnaire was administered before and after the first treatment session, before each treatment session, at the final treatment session, and 6 and 12 months after the final treatment session. Subjects were contacted by phone 2 to 3 days after each treatment session to monitor any adverse events; the clinical coordinator records all events on the CRF.

- Digital photography of treated areas was performed prior to each treatment, after the final treatment session, and again 6 and 12 months after the final treatment session. Additional photographs were to be taken in the event of an adverse reaction.

- Serum liver function tests, bicarbonate, (and in the case of elevated anion gap or decreased serum bicarbonate level, a serum lactate level) were drawn at the first treatment session, the third treatment session, and 6 months after treatment series completion.

A flow chart of procedures is noted in the following table.

Table 5.2 – Flowchart of Study Procedures

STUDY PHASE		TREATMENT PHASE				FOLLOW-UP PHASE	
Procedures \ Time point	Day 1	Week 4 (If needed)	Week 8 (If needed)	Weeks 12, 16, 20 (If needed)	Month 6	Month 12
Obtain Written Informed Consent	•					
Review Medical History and perform limited physical exam	•					
Review of Prior and Concomitant Medications / Treatments	•	•	•	•	•	•
Review of Inclusion and Exclusion Criteria	•					
Laboratory evaluations	•					
Investigator Rating of Lipoatrophy	•		•	•	•	•
Investigator Satisfaction with Outcome				•1	•	•
Treatment Procedure2	•	•	•	•	•	
Emotional / Psychological Impact of Lipoatrophy	•					
Pain / Discomfort of Treatment	•					
Subject Satisfaction with Treatment Outcome				•1	•	•
Adverse Event Assessment3	•	•	•	•	•	•
Serial Digital Photography4	•	•	•	•	•	•

1) Satisfaction obtained after treatment series completed.
2) Treatment sessions are 4 to 6 weeks apart with a maximum deviation of 10 days to a maximum total of 6 treatment sessions.
3) Subjects contacted by phone 2 to 3 days after each treatment session to monitor any adverse events.
4) Additional photographs taken in the event of an adverse event.

5.2 SELECTION OF STUDY POPULATION

All subjects enrolled have lipoatrophy of the face as a result of HIV and HIV antiretrovirals. The pattern of fat loss may involve the cheeks and/or the temples.

5.2.1 Inclusion Criteria

- Age > 18 years

- Lipoatrophy of the cheeks and/or temples of a severity of at least 1 on a scale of 1 to 5

- Willingness to sign informed consent for treatment

- HIV seropositive

5.2.2 Exclusion Criteria

- Active infection of the face

- Non-compliance based on prior history

- Active cutaneous Karposi's Sarcoma of the face

- Facial injections of any product within the last 3 months

- Active Herpes Labialis

- Skin condition of the face that is incompatible with the study treatment

- Active treatment with interferon or systemic corticosteroids

- Pregnancy or breastfeeding

- Signs or symptoms of lactic acidosis

5.2.3 Removal of Subjects from Therapy or Assessments

Treatment was stopped in the case of local skin reactions, intolerance, or on the request of the study subject.

5.2.4 Prior and Concomitant Treatments

Subjects have not received facial injections of any product within the 3 months prior to study entry. Subjects were not to be receiving active treatment with interferon or systemic corticosteroids.

5.3 STUDY TREATMENT

5.3.1 Description

New-Fill® is a resorbable skin implant in the form of a sterile suspension, which is reconstituted from a dry powder by the addition of sterile water for injection (SWFI). This suspension contains microparticles of Poly-L-Lactic Acid. It is a synthetic polymer that is biodegradable, biocompatible and immunologically inert. New-Fill® is supplied in vials of lyophilized product. The contents of each vial are reconstituted with 3 ml of sterile water for injection (SWFI). At the request of the subject for anesthesia, 0.5 cc of 2% lidocaine was substituted for an equal volume of SWFI in each vial, for a final volume of 3 cc total diluent per vial.

5.3.2 Treatment Assignment Methods

In this open-label study, all eligible subjects were assigned to treatment with New-Fill®.

5.3.3 Treatment Compliance

██████████ administered treatments via intradermal injection at 4 to 6-week intervals. Subjects received a minimum of one (1) to a maximum of six (6) treatment sessions, as determined by results and the agreement of the investigator and subject. All treatment sessions were recorded in the Treatment Record of the case report form (CRF) an in the standard clinic medical record.

5.4 STUDY ASSESSMENTS

5.4.1 Efficacy Assessment Methods

5.4.1.1 Investigator rating of Lipoatrophy:

The investigator rated the degree of lipoatrophy of the cheeks and the temples of each subject using a scale of 1 to 5, with 1 = mild and 5 = most severe. These ratings were based on a prescribed, printed scale. Ratings were performed before the first treatment, before the final treatment, and 6 and 12 months after the final treatment session.

5.4.1.2 Subject rating of Lipoatrophy:

The subject rated the degree of lipoatrophy of the cheeks and the temples using a scale of 1 to 5, with 1 = mild and 5 = most severe. The rating scale system was printed and presented to the subject for their use. Ratings were performed before the first treatment only.

5.4.1.3 Subject Satisfaction with Treatment Outcome:

The subject rated his satisfaction with treatment outcome on a scale of 1 to 5, where 1 = dissatisfaction and 5 = very satisfied. Ratings were performed at the final treatment, and 6 and 12 months after the final treatment.

5.4.1.4 Photography

Each subject was photographed prior to the first treatment and prior to each subsequent treatment session. In addition, each subject was photographed 6 and 12 months after the final treatment session and in the event of adverse reaction.

5.4.2 Safety Assessment Methods

5.4.2.1 Clinical Examination

A history and brief physical exam were performed at the baseline visit. Items noted in the subject medical records were: any inactive problems, current medications, allergies, family history, tobacco and alcohol use, review of systems, social history and assessment of the visit including vital signs and weight and follow-up plan.

5.4.2.2 Adverse Events

Adverse events related to the treatments were collected on all subjects. Subjects were asked to list any side effects noted from New-Fill treatment before each treatment session and at the 6 and 12 month follow-up visits. In addition, site personnel called the subjects 24-72 hours after each treatment session to monitor and record any adverse effects.

5.4.2.3 Injection Discomfort

Subjects were asked to rate the discomfort of the injection procedure immediately after the first injection. The subjects rated the discomfort on a scale of 1 to 5, where 1 = mildly painful and 5 = very painful.

5.5 CONCOMITANT MEDICATION

Collection of concomitant medications was noted for each subject at the baseline visit and recorded in the subject medical record. At each subsequent treatment visit subjects were asked if they had changed any medication or if they had taken any aspirin or anti-inflammatory medication in the last week.

5.6 TREATMENT COMPLIANCE

Subjects were scheduled to receive treatments at 4-week intervals. The majority of subjects were compliant with scheduling of treatments. However, due to travel and personal scheduling conflicts, some treatment intervals were at 4 to 8 week intervals. See section 6.2.

5.7 DATA QUALITY ASSURANCE

The Principal Investigator and the Clinical Coordinator at the designated study site collected data for all subjects.

All data were collected on the case record forms and in the standard medical records database of the study site. No outside audits of the data were performed. All data entered by subjects and the investigator on the CRF's and in the standard medical records were transposed onto digital spreadsheets by the Clinical Coordinator. The Principal Investigator verified each entry on the digital spreadsheets prior to data analysis.

6. STUDY POPULATION

6.1 DISPOSITION OF SUBJECTS

A total of 100 subjects were consented, with one subject not treated. The first subject was consented on 18 February 2002 and the final subject was consented on 27 March 2003. As of 18 September 2003, 95 of 99 subjects have completed their initial treatment series.

- 37 of 99 subjects completed their 6-month follow up. 24 subjects have missed this follow-up as of 18 September 2003.

- 34 subjects have completed their 12-month follow up.

The study is due to complete 12 months after the last treatment session for the initial series of treatments for subject number 100 (anticipated completion date: August 2004).

6.2 PROTOCOL DEVIATIONS

Many subjects in this study were living outside of the State of Florida. As such, scheduling and travel restrictions produced some variation in treatment intervals and follow up visits. Most subjects were able to complete their treatment sessions in the prescribed intervals; however, several subjects had one or more treatment sessions at 6 to 8 week intervals. Also, 6-month and 12 month follow-ups were performed via fax, e-mail, and telephone in several cases. In these cases, the mode of questionnaire completion was noted in the Case Report Form. When the subject was unavailable for 6-month laboratory evaluation, serum chemistries were requested of the primary care physician; again, these instances were noted in the Case Report Forms. Follow-

up digital photography was, of course, impossible for those subjects not physically present for follow up appointments.

Lack of product availability from the distributor ███████████ produced a 2 to 3 week delay in the treatment intervals for subjects actively receiving treatments at that time.

██

6.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographics collected for this study included: sex, age, history, physical, vital signs, laboratory evaluation of serum chemistries, liver function tests, serum bicarbonate and concomitant medications.

- 100 male subjects consented; 99 treated, 1 excluded for lactic acidosis

- Average age of subjects: 44.7 years (31 to 60 years)

- Average subject has been HIV + for 11.9 years (2 to 21 years)

- Average number of years on antiretroviral therapy 13 years (1 to 17 years)

TABLE 6.1: DISTRIBUTION OF AGE, EXTENT OF HIV AND ANTIVIRAL EXPOSURE

Demographic Measures	N = 99
Age (years)	
Mean	44.7
Min, Max	31, 60
Number of years with HIV	
Mean	11.9
Min, Max	2, 21
Number of years on Anti-virals	
Mean	13
Min, Max	1, 17

7. EFFICACY RESULTS

The results noted in this interim report reflect the data captured as of September 18, 2003, on 37 subjects who have completed the 6-month follow-up visit and 34 subjects who have completed the 12-month follow-up questionnaires.

7.1 OVERVIEW OF EFFICACY

Serial intradermal injections of New-Fill produce a significant cosmetic improvement in the facial defects seen in HIV-related lipoatrophy of the face.

7.2 PRIMARY PARAMETERS

Subjects rated their lipoatrophy at baseline on a prescribed, printed scale ranging from 1 (mild) to 5 (most severe). The average rating for the cheeks at baseline was 3.71 of 5 (N=99); the average rating for the temples at baseline was 3.03 of 5 (N=99). Seventy-seven subjects considered their cheeks and temples both effected, 22 considered their cheeks only to be effected.

The investigator rated facial lipoatrophy of the subjects at baseline and at subsequent visits on the same prescribed scale. Investigator Ratings are summarized on Table 7.2.

TABLE 7.2: INVESTIGATOR RATING OF LIPOATROPHY (1 to 5 scale)

	Baseline Visit	At Series Completion (Just prior to final treatment)	6 months after treatment	12 months after treatment*
No. of subjects	99	99	37	34
Cheeks	3.58	1.51	0.98	0.96
Temples	2.36	1.32	1.03	0.73

*includes 8 subjects who received one retreatment prior to the 12 month rating

7.2.1 Subject Satisfaction

Subject satisfaction with treatment outcome was rated on a scale of 1 (dissatisfaction) to 5 (very satisfied). The average satisfaction rating at the final treatment session was 4.71 (N= 94, 5 treated subjects did not complete this question at the appropriate visit time), 6 month after treatments the average rating was 4.79 (N=34), 12 months after treatments the average rating was 4.78 (N=34).

7.3 SECONDARY PARAMETERS

Subjects were asked to rate the discomfort of the New-Fill injection procedure immediately after the first treatment session on a scale of 1 (minimal pain) to 5 (severe pain). The average rating was 1.7 (N=99)

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The cosmetic filing effect from New-Fill treatments appears to be stable at least for 6 to 12 months, as evidenced by the Table 7.2. The average time to retreatment, with a single treatment visit requested by the subject, is 10.1 months (N=24), as of 18 September 2003. The average number of cc's of product used for retreatment in these cases was 6.5 cc.

8. SAFETY RESULTS

8.1 OVERVIEW OF SAFETY

In general New-Fill® injections appear to be safe and well tolerated by the HIV population. Adverse events are as expected with an injectable product and do not diminish subject satisfaction with the results.

8.2 EXTENT OF EXPOSURE

Of the 100 subjects who signed informed consent, 99 subjects received at least one treatment session. Subjects could receive up to a maximum of 6 treatment sessions during the course of the study. A summary of treatment sessions per subject is displayed in the following table.

TABLE 8.1 SUMMARY OF TREATMENT EXPOSURE (initial treatment sessions)

SESSION	# OF SUBJECTS
1 treatment	7
2 treatments	12
3 treatments	34
4 treatments	33
5 treatments	5
6 treatments	8
TOTAL	99

Subjects received an average of 7.8 cc of New-Fill® at each treatment session.

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8.3 ADVERSE EVENTS

8.3.1 Overview of Adverse Events

Two serious adverse events have been reported during the study and are outlined in section 8.4.3; neither was judged related to study treatment. Mild swelling and transient soreness are noted by many subjects after treatment. Small, palpable, but non-visible subcutaneous nodules are noted in 6% of subjects, with no subject describing these nodules as bothersome.

8.3.2 Display of Adverse Events

TABLE 8.2 SUMMARY OF ADVERSE EVENTS

Adverse Event	Total Events In 99 treated subjects
Adverse events reported	
Injection site swelling only	3
Injection site soreness and mild swelling	19
Injection site bruising	1
Transient Fever	2
Injection site nodule	6
TOTAL	31

8.4 DEATHS, DISCONTINUATIONS DUE TO ADVERSE EVENTS, AND OTHER SERIOUS ADVERSE EVENTS

8.4.1 Deaths

No deaths have occurred during the study.

8.4.2 Discontinuations Due to Adverse Events

No subjects have discontinued the study due to an adverse event.

8.4.3 Other Serious Adverse Events

Two serious adverse events have been reported in the study.

Subject ███████ had a prolonged interruption of his treatment due to the appearance and treatment of malignant melanoma on his abdominal wall. The lesion was noticed and biopsied 6 weeks following the subject's second New-Fill® treatment session. The subject underwent 2 Moh's surgery procedures and is 11-month post Moh's surgery at this time and the melanoma is considered resolved. The primary dermatologic surgeon did not consider the melanoma to be related to New-Fill® therapy, and the subject received 2 more New-Fill® treatment sessions, to complete his series, without complications.

Subject ███████ experienced de novo unstable angina 1 month after his second New-Fill® treatment and underwent immediate coronary artery bypass grafting for triple vessel coronary artery disease. The subject recovered quickly from CABG and was released from the hospital 7 days post surgery. This event was judged unrelated to New-Fill® administration by the primary care physician and the cardiologist, and the subject continued his treatment series after a 2-month delay.

The above adverse events were reported to ███████ to the FDA.

8.5 LABORATORY EVALUATION

Laboratory evaluation of serum chemistries, including liver function tests (LFTs), serum bicarbonate levels, and in the case of decreased serum bicarbonate or positive anion gap, serum lactate levels to determine if lactic acidosis is present are taken at subject screening (Day 1) and again 3 months after study initiation and 6 months after treatment series completion.

Transaminases:

Of the 100 subjects screened (Day 1), 10 were noted to have ALT greater then 2 times the upper limit of normal (mean ALT for these 10 subjects: 146, range 111-216). One of these subjects was excluded for lactic acidosis, as indicated below. Two subjects were known to have chronic Hepatitis C and had stable ALT reports for the 6 months prior to screening. The 7 remaining subjects with elevated ALT's were discussed with their primary care physicians and found to have chronic ALT elevations with negative acute viral hepatitis and liver ultrasound reports.

Serum ALT on the above 9 subjects was unchanged at month 3.

One subject with a serum ALT of 100 at screening had an ALT of 173 at month 3. The primary physician was contacted and it was discovered that this subject had a history of ALT elevations ranging from 120 to 180 over the past 3 years; viral Hepatitis screens and liver ultrasound were normal within the 6 months prior to New-Fill treatment. As this subject required only 3 treatment sessions, New-Fill treatment was not continued after the 3-month point.

Serum Bicarbonate/Lactate:

Serum bicarbonate was decreased (<22) in 4 subjects at screening. Reflex serum lactate was normal in all but one subject ███████. Subject ███████ was excluded from study, and the primary care physician was notified.

Serum bicarbonate was decreased in 2 subjects at 3 months; reflex serum lactate in both of these cases was normal. No subject has been found to have a decreased serum bicarbonate at the 6-month follow up as of 18 September 2003.

8.6 CLINICAL EVALUATIONS

A history and brief physical exam were performed at the baseline visit. Items noted in the subject medical records were: any inactive problems, current medications, allergies, family history, tobacco and alcohol use, review of systems, social history and assessment of the visit including vital signs and weight and follow-up plan.

9. PRELIMINARY RESULTS AND CONCLUSIONS

Serial intradermal injections of New-Fill® are safe, well tolerated, and effective for the treatment of HIV-associated lipoatrophy of the face.

There appears to be no effect on serum transaminases, serum bicarbonate, or serum lactate during the normal course of treatment with New-Fill® in HIV-positive subjects.

Side effects noted by subjects are similar to any other injection-based dermatologic procedure (transient soreness and mild swelling). There were no reported or observed cases of skin infections, herpes outbreaks, or hyperpigmentation at the treatment areas.

This protocol reports a low incidence of subject-reported non-visible, palpable subcutaneous nodules as compared to a prior report by the same investigator[16]. This diminution of subject reporting of these nodules may be related to more detailed pre-counseling of subjects regarding this side effect. As such, many subjects may have not reported subcutaneous nodules, as they were an anticipated possible side effect, which had been noted previously with this product.

Subject satisfaction with this procedure was very high. Subjects were very carefully counseled regarding expectations prior to treatment initiation. It was made clear that improvements seen with New-Fill® treatments were going to be slow and gradual, and that subjects should not expect complete resolution of any signs of lipoatrophy, especially in those subjects more severely effected. The importance of careful management of subject expectations cannot be stressed enough.

Optimal treatment intervals have yet to be established in the use of New-Fill® for lipoatrophy treatment. Treatment delays and interruptions appear to have little effect on the overall treatment outcome, as would be expected by the proposed mechanism of action of this product.

USE OF INTRADERMAL IMPLANTS OF NEW-FILL® IN PERSONS WITH HIV-ASSOCIATED LIPOATROPHY OF THE FACE

AN OPEN LABEL, SINGLE SITE STUDY

Protocol Number 002
Version: 19 February 2002

Principal Investigator

▮▮▮▮▮▮▮▮▮▮▮▮

Clinical Coordinator

▮▮▮▮▮▮▮

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CONTENTS

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13-069

STUDY SUMMARY

The goal of this study is to assess the efficacy and safety of the product New-Fill® (polylactic acid, poly-L-lactic acid) for the cosmetic treatment of HIV-associated lipoatrophy of the face.

All patients enrolled are expected to have lipoatrophy of the face as a result of HIV and HIV antiretrovirals. The pattern of fat loss may involve the cheeks and/or the temples.

1 – OBJECTIVES

1.1 Primary Objective
To evaluate the improvement of facial defects after serial intradermal injections of New-Fill®.

1.2 Secondary Objectives
-To evaluate the immediate and long term tolerability of New-Fill® intradermal injections.
-To evaluate the durability of the filling effect of New Fill intradermal injections.
-To evaluate the safety of New-Fill® intradermal implants in the setting of HIV-associated lipoatrophy of the face

2 - METHODOLOGY

This is an open label, uncontrolled, single center program. The duration of follow up with each patient will be 12 months after the final treatment session.

3 – ELIGIBILITY CRITERIA

3.1 Inclusion Criteria
-Age > 18 years
-Lipoatrophy of the cheeks and/or temples of a severity of at least 1 on a scale of 1 to 5 (Appendix D)
-Willingness to sign informed consent for treatment
-HIV seropositivity

3.2 Exclusion Criteria
-Active infection of the face
-Non-compliance based on prior history
-Active cutaneous Kaposi's Sarcoma of the face
-Facial Injections of any product within the last 3 months
-Active Herpes Labialis
-Skin condition of the face that is incompatible with the study treatment
-Active treatment with interferon or systemic corticosteroids
-Pregnancy or breastfeeding
-Signs or symptoms of lactic acidosis

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4 – STUDY SCHEMA

Patient presents with demonstrable facial defect desiring correction.

Intradermal New- Fill® Injections: The patient will receive facial intradermal injections with New Fill, using 1 ml to 9 ml of New- Fill® (0.15 g polyactic acid per 3 ml) per session. The typical treatment session involves injection of 6 ml of New-Fill®. Sessions will be 4 weeks apart. Patients will receive a minimum of one (1) and a maximum of six (6) treatment sessions, as determined by results and the agreement of the investigator and subject.

Serial Digital Photography: Each subject will be photographed prior to the first treatment session and before each treatment session. In addition, each subject will be photographed 6 and 12 months after the final treatment session, and in the event of an adverse reaction.

Questionnaires: Each subject will complete a questionnaire regarding treatment and tolerability before and immediately after the first treatment session, before the each treatment session, and after the final treatment session. Questionnaires will be completed 6 and 12 months after the final treatment session to establish durability of treatment response. The principal investigator will complete evaluation forms at each treatment session, and at 6 and 12 months after the final treatment session. Sample questionnaire and evaluation forms are included as Appendix A.

5 – STUDY ENDPOINTS

5.1 Primary Endpoint
Evaluation of the percentage of patients who have had satisfactory correction of facial defects as self-reported and recorded by serial photography.

5.2 Secondary Endpoints
-Summarize demonstrable effect of intradermal injections over the study period
-Summarize tolerability of injections by subject self-report
-Summarize adverse events

6– DURATION OF STUDY

24 months (2 years)

7 – SAMPLE SIZE

The study will be closed to accrual when sample size reaches 100 subjects.

8 – START OF STUDY

January 2002

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9 - INTRODUCTION AND RATIONALE

Lipoatrophy of the face has many known and many hypothesized mechanisms, including HIV disease, HIV antiretrovirals, and the aging process itself (1,2,3,4,5).

Multiple approaches have historically been used to correct these facial defects:

-Fat cell transplants by the Collman method have been used, but present technical difficulties with anesthetic and harvesting techniques. In addition the re-implanted tissue disappears at the same rate as the original loss through lipoatrophy.

-Non-biodegradable synthetic implants, the most common being silicone, present the disadvantage of possible immediate and delayed allergic responses and also the occurrence of inflammatory granulomas with possible rejection reactions (6).

-Other techniques use biodegradable implants. These are typically implants of animal origin, such as bovine collagen, which result in allergic reactions in 2-3% of all cases. These are re-absorbed particularly rapidly within a time span of several weeks to months (7,8,9). Bovine collagen implants produce no permanent filling effect.

New Fill® is a polyactic acid water gel (PLA), a synthetic polymer which is biodegradable, biocompatible and immunologically inert (10). New Fill is well tolerated and effective in past research (11). PLA has been used for many years in numerous therapeutic applications as resorbable suture material in ophthalmologic, neurologic, and thoraco-abdominal surgery. Materials for osteosynthesis and ligament repair have been developed around the PLA molecule.

PLA, the substance in New-Fill®, is widely used in aesthetic procedures, such as the treatment of facial wrinkles. New-Fill® has been approved by the French regulatory authorities since November 1999. Studies are ongoing to assess durability of response to PLA in facial aesthetics (12).

The evaluation of New-Fill® to correct facial lipoatrophy defects in persons with HIV disease is already underway in an international, multicenter study. Results thus far are encouraging, and adverse events have been rare (11,13). This investigator has also fully accrued subjects for a limited study of New-Fill® in this same population (14). Results thus far are very positive, and no serious adverse effects related to New-Fill® have been reported to this investigator to date.

10 – SUBJECT SCREENING

Screening evaluations will occur on Day 1, and will comprise:
-Clinical evaluation by Principal Investigator, History and Limited Physical
-Laboratory evaluation of serum chemistries, to include liver function tests (lft's), serum bicarbonate levels, and in the case of decreased serum bicarbonate or positive anion gap, serum lactate levels to determine if lactic acidosis is present.
-Consent Form explanation and witnessed consent
-Facial Digital Photography
-Pretreatment questionnaire
- In the case of a pre-menopausal female study subject, serum pregnancy testing will be completed prior to New-Fill® injections to exclude pregnancy. Last menstrual period will be recorded in the patient record. Methods of birth control will be discussed with the subject, and the chosen method of reliable birth control will be recorded in the subject record. The importance of not becoming pregnant during the study period will be emphasized to the subject.

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11 – TREATMENT AND MONITORING

Injections and monitoring:

-Each treatment will be provided by the Principal Investigator: injection at multiple sites with a total of 1 ml to 6 ml of New-Fill® in the middle layers of skin in the treatment area. Volume of New-Fill® injected at each treatment session will be subjective and tailored to produce filling of desired facial defects.

- Treatment sessions will be given at 4 week intervals, with a maximum variation of 10 days, to a maximum of 6 treatments in a single subject in the study period.

A small volume (0.5 cc) of 2% lidocaine may be added to the reconstituted New-Fill® product in place of an equal volume of sterile water at the request of the patient. The product manufacturer states that such inclusion of lidocaine is compatible with the product and may lessen patient discomfort.

Treatment will be stopped in the case of local skin reactions, intolerance, or on request of the study subject.

A patient questionnaire will be administered prior to each treatment session and at 6 and 12 months after the final treatment session. Patients will be contacted by phone 2 to 3 days after each treatment session to monitor any adverse effects, with events recorded by the clinical coordinator (see Appendix A).

Digital photography of treated areas will be performed prior to each treatment, after the final treatment session, and again 6 and 12 months after the final treatment session. Additional photos will be taken in the event of an adverse reaction. Serum liver function tests, bicarbonate, and, in the case of an elevated anion gap, a serum lactate level will be drawn 3 months after study initiation and 6 months after treatment series completion.

12 – ETHICAL CONSIDERATIONS

11.1 Data Collection
Monitoring will be performed by the Principal Investigator and the Clinical Coordinator at the designated study site.

11.2 Study Site
The only designated study site will be ███████████████████████████████

11.3 Confidentiality
The case record forms and study medication will be stored in a locked place, accessible only to the persons involved in the conduct of the study.

11.4 Regulatory Issues
The study will be conducted using consent procedures as detailed by the ████████████████████
████

11.5 Emergency Medical Services
A physician licensed to practice medicine in th█████████████ ll be on call and available 24 hours per day for study participants. ████████████████ major medical center, is located 0.5 miles from the study center and is available 24 hours per day for emergency services.

13 – DATA COLLECTION

At the completion of the study, data reported by patient questionnaires will be tabulated and summarized by the study personnel. Photographic images of subject progression will be made available to interested parties, provided adequate subject consent has been obtained for their distribution.

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14 - REFERENCES

1. Carr A, Samaras K, Chisholm J, Cooper DA. *Pathogenesis of HIV-1 protease inhibitor-associated peripheral lipodystrophy, hyperlipidemia, and insulin resistance.* Lancet 1998, 351 : 1881-3.
2. Gervasoni C, Ridolfo AL, Trifiro G, et al. *Redistribution of body fat in HIV-infected women undergoing antiretroviral therapy.* AIDS 1999, 13 : 485-471.
3. Saves M, Raffi F, Capeau J, Lang JM, Peyromond D, Basdevant A, Roloff S, Chene, G, and the APROCO Study Group. *Factors related to the presence of fat redistribution in HIV-infected patients treated with protease inhibitor containing regimens – APROCO Cohort.* 7th Conference of Retrovirus and Opportunistic Infections, San Francisco, January 30 – February 2, 2000.
4. Boufassa F, Dulioust A et al. *Lipodystrophy and metabolic disorders in 646 HIV-1 infected patients previously treated with or without protease inhibitors.* 7th Conference on Retrovirus and Opportunistic Infections.
5. Miller JE, Emery S, et al. *The Australian prevalence survey of lipodystrophy syndrome.* 7th Conference on Retrovirus and Opportunistic Infections.
6. Faure M. *Complications des implants de silicone et autres materiaux dits inertes.* Ann. Dermatol. Venerol. 1995, 122 : 455-459.
7. Stegman SJ, Chu S, et al. *A light and electron microscopic evaluation of Zyderm collagen and Zyplast collagen implants in aging human facial skin.* Arch. Dermatol. 1997, 123 : 1644-1649.
8. Pons-Guiraud A. *Reactions of delayed hypersensitivity with implants of bovine collagen. A study of 810 patients.* Nouv. Dermatol. 1992, 11 : 422-432.
9. Ghersetich I, Teofoli P, et al. *Ultrastructural study of hyaluronic acid before and after the use of pulsed electromagnetic field, electrorydesis, in the treatment of wrinkles.* Int. J Dermatol. 1984, 33 : 661-663.
10. Chadrashekar G, Udupa N, et al. *Biodegradable injectable implant systems for long- term drug delivery using ply (lactic-co-glycolic) acid copolymers.* J. Pharm. Pharmaco. 1996, 48 : 669-674.
11. Amard P, Saint-Marc T, Katz P. *The effects of polyactic acid (New Fill®) as therapy for lipoatrophy of the face.* 2nd International Workshop of Adverse Drug Reactions ad Lipodystrophy in HIV, Toronto, Canada, 13,14,15 September 2000.
12. Jacquet A, Moore N. *Evaluation of the Acceptability, Innocuity, and Performance f a Gel Made of Microshperes of Polylactic Acid –New-Fill®-for the Injection of Vertical Facial Wrinkles in Women.* Essais Cliniques Cosmetologie, Department de Pharmacologie, Universite Victor Segalen Bordeaux 2, Bordeuax, France, March 2001.
13. Katlama C, Johnson M, et al. *Study of the Safety and Efficacy of Intradermal Cheek Implants of Polylactic Acid in HIV Seropositive Patients with Severe Facial Wasting.* Study in progress. Sponsor: Hopital Pitie-Salpetriere, 47-83 Blvd de l'Hopital, 75013 Paris.
14. Engelhard P. *Compassionate Use of Facial Intradermal Implants of New-Fill® in Persons with HIV-Associated Lipoatrophy of the Face.* Study in progress.

15 – STUDY MEDICATION

New-Fill® will be purchased for the study by the Principal Investigator from the Manufacturer and its, Distributor. The address of the manufacturer is: Biotech Industry, S.A., 21 Rue Bernard HAAL, L 1711 Luxembourg, telephone 00 352 26 25 94 62, fax 00 352 26 25 94 60, internet www.new-fill.com. The principal Scientific Director of Biotech Industry, A.S., is ▇▇▇▇▇▇▇▇▇ a Doctor of Pharmacy. The distributor of New-Fill for North America is Farmaceuticos ▇▇▇▇▇▇ de Mexico, S.A,, Paseo de la Reforma, No. 509 11-D, Mexico 06500, D.F., telephone ▇▇▇▇▇▇▇▇▇▇▇, fax ▇▇▇▇▇▇▇▇, internet www▇▇▇▇▇▇▇▇ The Director of Farmaceuticos ▇▇▇▇▇▇ ▇▇▇▇▇▇

A New-Fill® product manuscript accompanies this protocol.

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Appendix A

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Use of New-Fill®   Protocol 002 Version 19 Feb 2002   **PT ID#** ☐ ☐ ☐ ☐ ☐

TO BE COMPLETED BY PATIENT

First Treatment Session Date_____

Age _____   Sex_____   # of years with HIV_____   # of years on Anti-virals _____

Areas affected by Lipoatrophy: Cheeks_____   Temples_____   Cheeks & Temples_____

	Cheeks:	Temples:
Severity of Lipoatrophy:	1= Mild	1= Mild
	5= Severe _____	5= Severe _____

Emotional / Psychological impact of Lipoatrophy: 1= Mild
                                                      5= Severe _____

Immediately After First Treatment Date_____

Pain / discomfort of treatment: 1= Mildly Painful
                                     5= Very Painful _____

At Second Treatment Date_____

1) Have you changed medications, taken aspirin or anti-inflammatory medication in the last week? If yes, please list:

_____

2) Side effects noted from New-Fill® treatment:_____

At Third Treatment Date_____

1) Have you changed medications, taken aspirin or anti-inflammatory medication in the last week? If yes, please list:

_____

2) Side effects noted from New-Fill® treatment:_____

If final treatment, satisfaction with treatment outcome: 1= Dissatisfied
                                                          5= Very Satisfied _____

At Fourth Treatment Date_____

1) Have you changed medications, taken aspirin or anti-inflammatory medication in the last week? If yes, please list:

_____

2) Side effects noted from New-Fill® treatment:_____

If final treatment, satisfaction with Treatment Outcome: 1= Dissatisfied
                                                          5= Very Satisfied _____

Use of New-Fill®   Protocol 002 Version 03 Jan 2002   **PT ID#** ☐ ☐ ☐ ☐ ☐

<u>**At Fifth Treatment**</u> Date_____

1) Have you changed medications, taken aspirin or anti-inflammatory medication in the last week? If yes, please list:
_____

2) Side effects noted from New-Fill® treatment:_____

_____

If final treatment, satisfaction with treatment outcome: 1= Dissatisfied
                                                          5= Very Satisfied _____

<u>**At Sixth Treatment**</u> Date_____

1) Have you changed medications, taken aspirin or anti-inflammatory medication in the last week? If yes, please list:
_____

2) Side effects noted from New-Fill® treatment:_____

_____

If final treatment, satisfaction with treatment outcome: 1= Dissatisfied
                                                          5= Very Satisfied _____

<u>**Six Months After Final Treatment**</u> Date_____

Side effects noted from New-Fill® treatment:_____

_____

Satisfaction with treatment outcome: 1= Dissatisfied
                                       5= Very Satisfied _____

<u>**Twelve Months After Final Treatment**</u> Date_____

Side effects noted from New-Fill® treatment:_____

_____

Satisfaction with treatment outcome: 1= Dissatisfied
                                       5= Very Satisfied _____

Study Doctor_____   Date _____

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Use of New-Fill®   Protocol 002 Version 19 Feb 2002   **PT ID#** ☐ ☐ ☐ ☐ ☐

TO BE COMPLETED BY DOCTOR/CLINICAL COORDINATOR

At First Treatment Session Date_____   If Female: result of pregnancy test_____

Date of Labs__/__/__   AST_____   ALT_____   Bicarb_____   Other_____
- *Investigator Rating of Lipoatrophy:* (1-5) Cheeks_____ Temples_____
Comment:_____

At Second Treatment Date_____
- *If final treatment, Investigator Rating of Lipoatrophy:* (1-5) Cheeks_____ Temples_____
Comment:_____

At Third Treatment Date_____
Date of Labs__/__/__   AST_____   ALT_____   Bicarb_____   Other_____
- *If final treatment, Investigator Rating of Lipoatrophy:* (1-5) Cheeks_____ Temples_____
Comment:_____

At Fourth Treatment Date_____
- *If final treatment, Investigator Rating of Lipoatrophy:* (1-5) Cheeks_____ Temples_____
Comment:_____

At Fifth Treatment Date_____
- *If final treatment, Investigator Rating of Lipoatrophy:* (1-5) Cheeks_____ Temples_____
Comment:_____

At Sixth Treatment Date_____
- *If final treatment, Investigator Rating of Lipoatrophy:* (1-5) Cheeks_____ Temples_____
Comment:_____

Six Months After Series Completion Date_____
Date of Labs__/__/__   AST_____   ALT_____   Bicarb_____   Other_____
- *Investigator Rating of Lipoatrophy:* (1-5) Cheeks_____ Temples_____
Comment:_____

12 Months After Series Completion Date_____
- *Investigator Rating of Lipoatrophy:* (1-5) Cheeks_____ Temples_____
Comment:_____

13-078

Use of New-Fill®   Protocol 002 Version 3 Jan 2002   **PT ID#** ☐ ☐ ☐ ☐ ☐

Telephone Log (24-72 hours after each treatment)

Date___/___/___Comments:_____

Date___/___/___Comments:_____

Date___/___/___Comments:_____

Date___/___/___Comments:_____

Date___/___/___Comments:_____

Date___/___/___Comments:_____

Study Doctor_____ **Date**_____

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Appendix B

ADVERSE EVENTS   EVENT # [|]

▶Where there any significant adverse events since the first adminstration of study drug?

[ ] Yes [ ] No

(If yes complete below)

▶Describe the adverse event: _____

▶Is the event serious? [ ] Yes   ▶ Is the event intermittent? [ ] Yes [ ] No

[ ] No   ▶Ongoing? [ ] Yes [ ] No

▶Date of Onset [| |] [| |] [| | | |]
           M M   D D   Y Y Y Y

▶Date resolved [| |] [| |] [| | | |]
           M M   D D   Y Y Y Y

▶Duration if less than 24 hours [| |] [| |]
                              H H   M M

▶Relation to study drug [ ] Probable
[ ] Possible
[ ] Unlikely

▶Severity [ ] Grade 1/Mild
[ ] Grade 2/Moderate
[ ] Grade 3/Severe
[ ] Grade 4/ Life-threatening

▶Was the study drug [ ] Continued unchanged
[ ] Dose regimen modified/interrupted
[ ] Discontinued permanently
[ ] Not applicable

▶Were any medical or surgical interventions needed to resolve adverse reaction? If yes, describe:

_____

▶Was the patient hospitalized as a result of the adverse event? [ ] No [ ] Yes

▶ Date of admission [| |] [| |] [| | | |]
                M M   D D   Y Y Y Y

▶ Date of release [| |] [| |] [| | | |]
            M M   D D   Y Y Y Y

Study Doctor _____   Date _____

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Appendix C

C13

Use of New-Fill®
Apex Protocol #002
Version: 19 February 2002

Treatment Record

Pt. ID# ☐ ☐ ☐ ☐ ☐

Date	Site(s) Injected	Total cc's New-Fill	Comment

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Appendix D

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Rating of Lipoatrophy

To date, there is no established rating system to classify HIV-associated facial lipoatrophy. No studies have been performed to establish validity of any rating system or scoring scale. The use of facial ultrasound has been used to establish dermal and fat layer thickness before and after New-Fill® treatment: however, the validity of this method has yet to be evaluated (ref 11,13).

The principal investigator has over 8 years of experience in treating patients with HIV, and, as a result, has learned to identify facial lipoatrophy of varying degrees of severity. Patients themselves effectively identify lipoatrophy, and can compare themselves with their peers to assess severity. The overall goal with any method for treating facial lipoatrophy is the improvement in the patient's perception of the facial defects; the most important indicator of treatment success in a cosmetic procedure is the rating of patient satisfaction with treatment outcome.

With these points in mind, both the patient and the principal investigator will use the lipoatrophy rating scale presented on the following page for rating severity of lipoatrophy appearance both before and after the treatments series. Equally important in determining effectiveness of the treatments will be the patient's rating of satisfaction with treatment outcome.

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13-085

Lipoatrophy Rating Scale

We will be using a scale to rate facial lipoatrophy on a scale of 1 to 5, with 5 representing the most severe facial fat loss. Fat loss may effect the cheeks, the temples, or both to varying degrees. The principal investigator will describe medical terminology in the scale to patients in language they will understand.

Grade 1 = (Mild) Presence of indentation line in central cheek running parallel and lateral to line of nasolabial folds (laugh lines). Prominence of bone in lateral eyebrow area; mild concavity of temple area.

Grade 2 = (A point between grade 1 and grade 3)

Grade 3 = (Moderate) Mid and medial portions of zygoma become more visible. Indentation in central cheek lateral to nasolabial more prominent, and may extend from mid-lateral nasal area to superior aspect of mandible. Prominence of bone in brow extends to mid brow area, with deepening of concavity in temples extending laterally towards the pinna.

Grade 4 = (A point between grade 3 and grade 5)

Grade 5 = (Severe) Profound depression of the mid face and malar area, with distinct prominence of the entire length of the zygoma. There is profound indentation of tissue along the inferior aspect of the zygoma. Facial musculature, especially the masseter muscle, is often plainly visible. Veins are often prominent in the skin below the eyes and especially in the temple area. The borders of the parotid gland are often prominent due to global lack of subcutaneous fat. The temple is profoundly depressed and the bones of the lateral zygoma and entire brow line are grossly prominent. The eyes appear "sunken" as fat around the orbit has been lost.

C17

DATE	PATIENT LOG

DATE   SIGNATURE

INTERIM STUDY REPORT

SAFETY, EFFICACY AND IMPACT OF INTRADERMAL NEW-FILL® IMPLANTS IN PERSONS WITH HIV-ASSOCIATED LIPODYSTROPHY

Principal Investigator: ███████████████

Co-Investigator: ██████████████

Study Site: ███████████████████

Version Date: September 9, 2003

Version Number: 1.0 – Final

INVESTIGATOR STATEMENT:

To the best of my knowledge, the information contained in this interim report accurately reflects the patient status during the conduct of this study.

_____ 9- 9-03
                         Date

_____ 9-9-03
                         Date

TABLE OF CONTENTS

1.   INTRODUCTION

This report presents interim data from an ongoing clinical trial. This trial was conducted under an Investigator Initiated Treatment IDE (███████████). This interim report summarizes the data that has been collected as of June 30, 2003.

1.1   BACKGROUND

Facial lipodystrophy has many known and also several hypothetical causes. Initially thought to be a side effect of the class of medications known as protease inhibitors, it is felt to be multi-factorial including HIV itself, HIV antiretrovirals and the aging process itself[1-5]. Regardless of the cause, the effects of facial wasting on patient's overall mental health can be significant[6]. In addition, as HIV/AIDS patients are living longer with advances in medicine, the problem of how to effectively treat HIV-Associated Lipodystrophy has become more critical.

Multiple approaches have been attempted to address this problem. Some of these treatments are approved for use in this country while others are offered in foreign countries in sometimes-unregulated settings.

Biodegradable implants: These can be broadly put in two categories: animal origin and human origin. The oldest of these is Bovine collagen. Although this product has the longest clinical usage, it carries a 2%-3% incidence of allergic reaction due to the foreign protein content. In addition, the amount needed for correction for facial wasting is significant, rather costly and the resorption of the material is particularly rapid in the order of several weeks to months[7,8] and offers no permanent filling effect. Hyaluranate gels have a very rapid absorption by the body that limits their cosmetic use[9]. More recently, collagen implants of the human origin (Cymetra™, Fascian™) have become available. Results with these products have been disappointing.

Non-biodegradable synthetic implants; including silicone oil and Polymethylmethacrylate (PMMA) beads. Silicone has the problem of inflammatory granuloma formation, sometimes years after insertion as well as the chance of migration of product[10]. PMMA is placed in a bovine collagen solution, which carries the chance of allergic reaction[11, 12] Non-biodegradable implants do not allow for the possibility of cosmetic adjustments after insertion afforded by the biodegradable implants.

Fat cell transfer/transplant: In addition to the technical difficulties in harvesting sometimes-limited fat in HIV patients, the reimplanted tissue tends to disappear at the same rate as the original fat loss due to lipoatrophy[13].

1.2   RATIONALE

New-Fill®, poly-L-lactic acid hydrogel (PLA) is a synthetic polymer, which is biodegradable, biocompatible and immunologically inactive[14]. As a synthetic polymer, PLA contains no products of animal origin which rules out any risk of viral or prion contamination. Past research has shown PLA to be well tolerated in HIV patients[15]. PLA has a long track record of use in a

variety of medical applications such as resorbable suture material used in neurologic, ophthalmologic and abdominal surgeries[16]. Fixation devices have been created for ligament and bony repair[17-20], utilizing the PLA molecule. PLA has been used as the vector for sustained release of medication administered orally and parenterally (subcutaneous, intramuscular). The temporary entrapment of the drug within a bioabsorbable polymer matrix ensures that the active substance is protected and gradually released in a controlled manner as the polymer hydrolyzes[21-25]. PLA is widely used outside the USA for a variety of aesthetic procedures such as treatment of facial rhytides. Studies have been conducted to evaluate the long-term durability of PLA in facial aesthetics[26].

The evaluation of New-Fill to correct HIV-Associated Lipodystrophy has been noted in several international studies[15, 27-30]. Results are encouraging and adverse events appear to be rare[15, 27-29]. New-Fill has been used in this country under compassionate usage guidelines for persons with HIV disease with equally promising results[31].

2.   STUDY OBJECTIVES

Primary:

To evaluate the quantifiable improvement in facial wasting (Lipodystrophy) after serial intradermal injections of New-Fill.

Secondary:

- To evaluate the safety of New-Fill usage in repeated treatments in patients with HIV/AIDS.

- To evaluate the long-term (greater than 6 months) durability of the increase in skin thickness.

- To evaluate the immediate and long-term patient acceptance of serial treatments of New-Fill.

- To evaluate the psychological impact of treatment of HIV-Associated Lipodystrophy with New-Fill intradermal injections.

3.   ETHICS

The study was conducted in compliance with the Institutional Review Board (IRB) and informed consent regulations set forth in the US Code of Federal Regulations (CFR) 21, Part 56, and in CFR 21, Part 50, respectively. The protocol was submitted to an independent IRB for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study was made in writing to the investigator and a copy of their decision was provided to the investigator/sponsor before commencement of the study. The IRB consulted for this study was: ██, chairman: ████████████████

This study is being conducted according to International Conference on Harmonization (ICH) standards of Good Clinical Practice (GCP) guidelines, and in agreement with the latest revision of the Declaration of Helsinki, as well as applicable local regulations.

4. INVESTIGATORS AND ADMINISTRATIVE STRUCTURE

███████████████████████ with Principal Investigator ████████████ and Co-Investigator ██████████████ are conducting the study at ███████████ ███████████████

██████████ is now performing monitoring duties as defined in the IDE in place of ████████ ████████. These duties include ensuring that the study is conducted in accordance with the investigational plan and that all consents, forms and data are entered at each visit.

5. INVESTIGATIONAL PLAN

5.1 OVERALL STUDY DESIGN

This is a single site, open label design study. Patients act as their own controls. After written informed consent, patients undergo initial screening to include: baseline buccal skin thickness (determined by calipers at standard points bilaterally), laboratory evaluations (includes: serum chemistry, liver function tests, serum bicarbonate, serum lactate, PT/PTT, and CBC with differential), baseline digital photography, Psychological Well-Being Questionnaire, and study questionnaire.

Patients receive intradermal injections of New-Fill into targeted treatment areas using 1 ml to 6 ml of reconstituted New-Fill (50 mg of poly-L-lactic acid per ml) per session. A typical treatment session involves injecting 6 ml of the product. Sessions are scheduled 3 weeks apart with an allowable variability of 10 days. Patients receive a minimum of 1 to a maximum of 6 treatment sessions, as is mutually agreed necessary by the injecting physician and the patient. During the study period and for 12 months following the last treatment session, buccal skin thickness is measured as well as other study parameters. Specifically, digital photography and caliper skin thickness is measured prior to each treatment session. Laboratory studies are done at 3-month intervals during the active phase and at 6 month and 12 months following the final treatment session. Study questionnaires are completed by the patients and treating physicians after each treatment session and at 6 and 12 months post treatment. Psychological Well Being Questionnaires are completed at the end of treatment and at 6 and 12 months following completion of treatment.

5.2   STUDY ASSESSMENTS

5.2.1   Screening evaluations

The following evaluations occurred on Day 1:

- Clinical evaluation by the study investigators (History and limited physical examination)

- Laboratory evaluation of serum chemistries, including liver function tests (LFTs), serum bicarbonate levels, serum lactate, PT/PTTT, and CBC with differential.

- Study process and procedures including Consent Form explanation and witnessed consent.

- Facial Digital Photography

- Initial Caliper skin thickness measurement

- Baseline Psychological Well Being Questionnaire (Included in Protocol)

- Pre-menopausal female study patients had serum pregnancy testing prior to New-Fill injections to exclude pregnancy. In addition, the importance of not becoming pregnant during the study period was emphasized to the patient.

5.2.2   Injections and monitoring

The following procedures were completed at the treatment sessions and/or follow-up visits:

- ██████████████ provide each treatment: Injections were performed subdermally at multiple sites with a total of 1 ml to 6 ml of New-Fill to the marked treatment area. Volume of New-Fill injected at each treatment session is subjective and individualized to produce the desired filling effect for that patient based on the investigators previous experience. No more than 6 ml of reconstituted New-Fill are used at any one-treatment session.

- Treatment sessions are 3-weeks apart with a maximum deviation of 10 days, to a maximum total of 6 treatment sessions in a single patient during the study period.

- Caliper skin thickness measurements are performed prior to each treatment, after the final treatment and 6 and 12 months after final treatment.

- Patient questionnaires regarding acceptability of treatment are administered at each treatment session and at 6 and 12 months after final treatment to determine overall satisfaction and perceived durability of the device. Patients are contacted by phone within 48-72 hours after each treatment to monitor any adverse events; the investigator or study monitor records all events on the CRF.

- Digital photography of treatment areas are performed prior to each treatment session, after final treatment, and again 6 and 12 months after the final treatment. Additional photographs are taken in the event of an adverse reaction.

- Laboratory studies (serum chemistries, LFTs, serum bicarbonate levels, serum lactate, PT/PTTT, and CBC with differential) are performed every 3 months during treatment and at 6 and 12-month follow-up appointments following the final treatment.

- Psychological Well Being Questionnaires are completed by the patients at the end of treatment and 12 months after the final treatment. Patients act as their own control regarding validity of the study questionnaire.

A flow chart of study procedures is noted in the following table.

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Table 5.1 – Flowchart of Study Procedures

Time point / Procedures	BASELINE AND TREATMENT PHASE					FOLLOW-UP PHASE	
	Baseline	Initial Treatment Visit	Week 3 (if needed)	Week 6 (if needed)	Weeks 9, 12, 15 (if needed)	Month 6	Month 12
Obtain Written Informed Consent	●						
Review Medical History and perform limited physical exam	●						
Review of Prior and Concomitant Medications/Treatments	●		●	●	●	●	●
Review of Inclusion and Exclusion Criteria	●						
Treatment Procedure[1]		●	●	●	●		
Adverse Event Assessment	●	●	●	●	●	●	●
Telephone contact[2]		●	●	●	●		
Serial Digital Photography[3]	●		●	●	●	●	●
Skin Thickness Measurement[4]	●		●	●	●	●	●
Psychological Well Being Questionnaire[5]	●						●
Laboratory Studies	●				●	●	●
Study Questionnaire	●		●	●	●	●	●

1) Treatment sessions are 3 weeks apart with a maximum deviation of 10 days to a maximum total of 6 treatment sessions.
2) Patients are contacted within 48-72 hours after each treatment to monitor for adverse events.
3) Photographs are taken at baseline and prior to each treatment session and in the event of an adverse event.
4) Skin thickness measurements are taken at baseline and prior to each treatment session.
5) Questionnaire taken prior to treatment, at the end of treatment, and 12 months after the final treatment.

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5.3 SELECTION OF STUDY POPULATION

Patients entering the research study are HIV+ with clinically significant lipodystrophy.

5.3.1 Inclusion Criteria

Patients fulfilling the following criteria were eligible for inclusion:

- Age >18

- Lipodystrophy of the cheek/temple of a degree that is bothersome to the patient i.e. clinically significant

- Willingness to participate actively in the study

- HIV seropositive

5.3.2 Exclusion Criteria

A patient fulfilling any of the following criteria was ineligible for inclusion:

- Facial injections of any substance within the last 3 months

- Active infection of the face

- Active Karposi Sarcoma involving the treatment area

- Active treatment with interferon or systemic corticosteriods

- Pregnancy or breast feeding

- Non-compliance based on history or previous experience

- Signs or systems of lactic acidosis

- Known preexisting renal disease

- Poorly controlled Diabetes Mellitus

5.3.3 Removal of Patients from Therapy or Assessments

Treatment sessions were stopped in the case of local skin reaction, infection, patient intolerance, significant and unexplained changes in laboratory values and on the request of the patient.

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5.3.4 Prior and Concomitant Treatments

Patients were not allowed to have received facial injections of any substance within the 3 months prior to study entry. Patients could not be receiving active treatment with interferon or systemic corticosteroids.

5.4 STUDY PRODUCT

5.4.1 Description

New-Fill is a resorbable skin implant in the form of a sterile suspension, which is reconstituted from a dry powder by the addition of sterile water for injection (SWFI). This suspension contains microparticles of Poly-L-Lactic Acid. It is a synthetic polymer that is biodegradable, biocompatible and immunologically inert. New-Fill is supplied in vials of lyophilized product. The contents of each vial are reconstituted with 3 ml of sterile water for injection (SWFI).

5.4.2 Treatment Assignment Methods

In this open-label study all eligible patients are assigned to treatment with New-Fill.

5.4.3 Treatment Compliance

Treatments are administered via intradermal injection by ▓▓▓▓▓▓MD or▓▓▓▓▓▓MD at 3-week intervals with an allowable variability of 10 days. Patients receive a minimum of one (1) to a maximum of six (6) treatment sessions, as is mutually agreed necessary by the injecting physician and the patient. All treatment sessions are recorded in the patient chart and case report form.

5.5 STUDY ASSESSMENTS

5.5.1 Efficacy Assessment Methods

5.5.1.1 Skin Thickness Measurements

Each patient had baseline caliper skin thickness determined at bilateral fixed points located at the intersection of the vertical axis through the lateral canthus of the eye and the horizontal axis of the nares. Caliper skin thickness is determined prior to subsequent treatments, and at 6 months and 12 months following the final treatment session.

5.5.1.2 Investigator Rating of Lipoatrophy

At the baseline visit the investigator will examine the patient and determine caliper skin thickness and rate the patient's degree of lipoatrophy as: mild, moderate or severe.

5.5.1.3 Psychological Well Being Questionnaire

Each patient completes initial questionnaires ascertaining patient feelings regarding overall health, emotional well-being, and effects of HIV-Associated Lipodystrophy. Patients complete the same questionnaire at the end of the treatment and 6 and 12 months after the final treatment. Patients will act as their own controls regarding validity of the study questionnaire.

5.5.1.4 Serial Digital Photography

Each patient is photographed in the sitting position using AP and lateral oblique technique at a distance of three feet. Photographs are taken prior to the first session and before each subsequent treatment session. Additional photographs are taken at 6 and 12 months after the final treatment and in the event of an adverse event.

5.5.1.5 Acceptability of Treatment

Each patient completes a questionnaire regarding the acceptability of treatment at each treatment session. Patients also complete questionnaires at the end of treatment and at 6 and 12 months following the final treatment to determine overall satisfaction and perceived durability of the device. Investigators also complete evaluation forms at each treatment session and at 6 and 12 month follow-up visits. At the 6 and 12 month follow-up visits patient were also asked if they would recommend this treatment to a friend (patients checked "yes" or "no").

5.5.2 Safety Assessment Methods

5.5.2.1 Clinical Evaluation

A history and brief physical exam were performed at the baseline visit. Items noted in the subject medical records were: Age, sex, current medications, allergies, number of years with HIV, number of years on antiretrovirals and severity of lipoatrophy (mild/moderate/severe). Photographic review by both investigators was later performed to correlate severity of Lipoatrophy against the published James Classification[32].

5.5.2.2 Laboratory Studies

Initial laboratory studies include serum chemistries, liver function tests (LFT'S), serum bicarbonate, serum lactate, PT/PTT, and CBC with differential. Laboratory studies are repeated every three months during treatment and at 6 and 12-month follow-up appointments following the final treatment.

5.5.2.3 Adverse Events

Adverse events related to the treatments were collected on all patients. Patients were asked to list any side effects noted from the New-Fill treatment after each treatment session and at the 6 and 12 month follow-up visits. Unrelated events were also captured.

5.5.2.4 Injection Discomfort

Patients were asked to rate the discomfort of the injection procedure immediately after the first injection. The patients rated the discomfort on a scale of 1 to 5, where 1 = mild and 5 = severe.

5.6   CONCOMITANT MEDICATION

The collection of concomitant medications was noted for each patient at the baseline visit and recorded in the patient medical record. Although not part of the original protocol, subsequent medication changes were not specifically elicited but collected if described by the patient.

5.7   TREATMENT COMPLIANCE

Patients were scheduled to receive treatments at 3-week intervals plus a ten-day window. The majority of patients were compliant with the visits, however one patient was treated at an 8-week interval due to a family emergency.

5.8   DATA QUALITY ASSURANCE

The study Investigators and the study monitor at the designated study site collected data for all patients.

All data were collected on the case record forms and in the clinical database of the study site. No outside audits of the data were performed, due to patient confidentiality

6.   STUDY POPULATION

6.1   DISPOSITION OF PATIENTS

A total of 95 patients consented for participation in the study. The first patient was consented on 7/23/02 and the last patient was consented on 6/30/03. Since the study is currently ongoing, a breakdown of patient disposition as of June 30, 2003 is as follows:

- 8 patients consented and not yet treated

- 53 patients completed treatment series, of which

    o   15 patients completed 6 month follow-up

    o   5 patients missed their 6 month follow-up and were contacted by phone

- 33 patients ongoing treatment

- 1 patient had his treatment discontinued due to a significant protocol deviation

6.2 PROTOCOL DEVIATIONS

One patient had treatment that later was discovered to not be HIV +. The initial lab work required for the study did not involve viral load or T-cell count. The patient had previous New-Fill® treatments done in Mexico and knew of the study inclusion criteria. On subsequent treatment and medication review it was noted that he was not on any medication and he then offered that he was not HIV positive. He was discharged from the study after 1 treatment. As mentioned, one patient was treated at an 8-week interval. Four patients had labs over 30 days before their first treatment.

6.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographics collected for this study included: sex, age, history, physical, laboratory evaluation of serum chemistry, liver function tests, serum bicarbonate, serum lactate, PT/PTT, CBC with differential, and concomitant medications. As of 6/30/03:

- 86* treated patients included: 84 male patients and 2 female patients

- Average age of patients: 44.9 years (32 to 65)

- Average patient has been HIV + for 13.1 years (3 to 22)

- Average number of years on antiretroviral therapy 9.3 years (2 to 22)

TABLE 6.1: DISTRIBUTION OF AGE, SEX, AND RACE

Demographic Measures	N=86
Age (years)	
Average	44.9
Min, Max	32, 65
Race	
Caucasian	74
Black	4
Hispanic	6
Other	2
Number of years with HIV	
Average	13.1
Min, Max	3, 22
Number of years on Antiretrovirals	
Average	9.3
Min, Max	2, 22

*1 patient (43 year old Caucasian male) discontinued due to NON-HIV status not included in this demographic data, as this would skew the number of years with HIV and number of years on antiretrovirals.

7. EFFICACY RESULTS

The results noted in this interim report reflect the data captured on 15 patients who have completed the 6 months follow-up visit as of June 30, 2003. The 5 patients who missed their 6 months follow-up appointments were contacted by phone and a verbal report of efficacy and satisfaction was obtained. They will be reported individually however they will not be included in the measurement data as none could be obtained on them at this time.

7.1 OVERVIEW OF EFFICACY

Based on the data collected to date, the device, New-Fill® is highly effective as a treatment for HIV-Associated Lipoatrophy. Most patients required between 3-6 treatments to obtain satisfactory correction as determined by both patient and physician. A few patients (8%) with the most severe lipoatrophy could have used more than 6 treatments but were limited by the study design.

7.2 PRIMARY PARAMETERS

Skin calipers, as described in the protocol, were used to measure skin thickness at fixed points. Each investigator measured only his or her own patients. On examination of the data, a large range (0.5-11mm) was observed in increased skin thickness at 6 months. Further evaluation revealed a difference in the general initial skin thickness between investigators. Although Dr. ██████ patients had a slightly more severe degree of lipoatrophy (Average James Scale 3.2 versus 2.4 for Dr ██████ patients) this probably also represented a slight difference in measuring technique. As each investigator only measured his or her own patients, the change in thickness for each patient was felt to be reliable (intra-patient) however, the inter-patient variability is large enough that the data is presented for each investigator. Assuming that the measuring technique of each investigator was constant throughout the study, although the absolute numbers may be variable, the percent change from baseline would better express the cumulative change in skin thickness for the entire group.

INVESTIGATOR: ██████ (n=6)

Avg. mm Initial	5.54 mm
Avg. mm end of Treatment	6.88 mm
Avg. mm 6month FU	7.13 mm
Avg. mm increase at 6 months	1.59 mm

INVESTIGATOR ███ (n=9)

Avg. mm Initial	7.44 mm
Avg. mm End of Treatment	13.92 mm
Avg. mm 6 month FU	13.22 mm
Avg. mm increase at 6 months	5.78 mm

The combined, weighted, average increase in skin thickness for all 15 patients was 66.0% from baseline and was maintained, 61.4%, at 6 months.

As stated, 5 patients missed their 6-month follow-up appointments for a variety of reasons. Two patients were out of town on business, one was ill with neurologic lower extremity problems, one patient was "feeling ill" and did not want to travel to the office since he was happy with his results. The final patient did not feel it was necessary for him to follow-up, as he had no questions or problems. Phone interviews with these patients revealed that all were satisfied with their treatments (Average satisfaction score of 4.5) and 100% would recommend this treatment to a friend. Two of the five thought that there may have been some increase in correction since their final treatment and the remainder felt that they had retained about the same amount of correction. Since the investigators could not independently verify these results, their results were not included in the 6-month follow-up data.

7.3 SECONDARY PARAMETERS

Interim Data reveal:

- Patient satisfaction: On a scale of 1-5 with 1 being Dissatisfied and 5 being Very Satisfied, patients reported an average satisfaction score of 4.7 at the end of treatment and 4.5 at 6 months. Physician Satisfaction with overall correction was 4.7 at the end of treatment and 4.7 at 6-month follow-up.

- Patients verbally reported an increase in confidence and improved self-image with treatment. Due to the design of the well being questionnaire, statistical correlation is difficult to obtain. The vast majority of patients were happy with their lives and glad to be alive so this did not change with treatment. The trend was for patients to be less sad with treatment and to feel that their facial appearance better reflects the state of their overall health.

- Patients reported an average pain score of 1.7 on a 1-5 scale (5 maximum pain) for the treatment session. In general, patients found the treatments tolerable as no patient requested to discontinue treatment. 100 % of patients would recommend this treatment to a friend.

8. SAFETY RESULTS

8.1 OVERVIEW OF SAFETY

Overall, in the patients treated to date, the safety profile of New-Fill® has been very favorable. There were no serious adverse events. Most patients experienced swelling for a few days related to the treatment technique. Bruising occurred in 27 of 87 patients (31.0%). In these 27 patients, however, bruising only occurred in 36 of 122 treatment sessions. The bruising was self limited and not bothersome to patients. The most significant adverse event was small nodule formation that occurred in 8 of 87 patients. Three of these nodules resolved by the end of treatment and two more resolved by 6-month follow-up. None of the nodules were bothersome to patients. One patient who has chronic passive Hepatitis B did not have any change in his liver function tests over the 6-month follow-up period.

8.2 EXTENT OF EXPOSURE

Of the 95 patients who signed informed consent, 87 patients received at least one treatment session as of 6/30/03. The remaining patients are awaiting their first treatment. Patients could receive up to a maximum of 6 treatment sessions during the course of the study. An interim summary of treatment sessions per patient who have completed treatment is displayed in the following table.

TABLE 8.1 SUMMARY OF NUMBER OF TREATMENTS FOR COMPLETED PATIENTS

SESSION	# OF PATIENTS
1 treatment	1*
2 treatments	3
3 treatments	11
4 treatments	6
5 treatments	11
6 treatments	22
TOTAL	54

* 1 patient had a single treatment and was discontinued - did not meet inclusion criteria

The average amount of product injected at each session was 6 cc.

8.3 ADVERSE EVENTS

8.3.1 Overview of Adverse Events

No serious adverse events have been reported during the study. Injections related adverse events include: mild to moderate pain (9.2 %) and mild transient bruising (31.0%). Small, non-visible subcutaneous nodules have been noted (9.2%).

8.3.2 Display of Adverse Events

TABLE 8.2   SUMMARY OF TREATMENT RELATED ADVERSE EVENTS

Preferred Term	Total Events N=87
Adverse events reported	
Injection site pain (persistent)	8
Injection site bruising	27
Injection site nodule	8
Total	43

8.3.3 Unrelated Adverse Events

Three patients had isolated changes in blood sugar at various times throughout the study period. No specific pattern of change could be established. The investigators and primary care physicians felt that these were isolated changes and not related to the device.

- 1 patient had an elevated baseline glucose of 172-mg/dl, which was increased at 3 months and then returned to normal at 6-month follow-up.

- 1 patient had a slightly elevated baseline glucose of 135 mg/dl, normal three-month blood glucose and then elevated level at 6-month follow-up.

- 1 patient with normal blood glucose throughout the study had a slightly elevated blood glucose at the 6-month follow-up. His primary care physician noted this to be a non-fasting sample.

- 1 patient had a sinus infection. This patient has a history of sinus infections. His treating Otolaryngologist did not feel that this was device related.

- 1 patient had superficial redness around the injection sites that was treated with topical antibiotic cream with resolution over 2 days.

- 1 patient experienced possible kidney pain for 1 week but was later felt to be lower back pain/strain by his primary care physician.

- 1 patient experienced decrease taste sensation to sweet. This occurred approximately 2 weeks after each of the first two treatment sessions. His taste recovered spontaneously by the fifth treatment session (3 months) and remains normal at this point.

TABLE 8.3   UNRELATED ADVERSE EVENTS

Event	Total events N=87
Increase Blood Glucose	3
Superficial Redness	1
Sinus Infection	1
Decrease Taste	1
Kidney area pain	1
Total	7

8.3.4   Serum Lactate Levels

Serum venous lactate levels were wide ranging. This most likely reflects the inherent difficulty with specimen collection with this test rather than actual clinically significant changes. One patient, for example, had a level of 34.2 mg/dl at three-month follow-up. A repeat blood draw only 5 days later gave a result of 18.4 mg/dl from the same laboratory. The patient had no symptoms or change in medication between tests. In addition, different laboratories have different normal ranges making comparison of absolute numbers difficult. No patients during the study, to date, have expressed symptoms of clinical lactic acidosis (vomiting, malaise, muscle aches).

Five patients showed an increase in serum venous lactate at some point during the study.

1) R.E.- increase from 10 mg/dl (3-12 mg/dl) to 16 mg/dl at 6 months. There was no change in anion gap ruling out acidosis and no clinical symptoms. Not felt to be clinically significant.

2) B.Z.- level 9.2 mg/dl (5-20mg/dl) at baseline, increase to slightly above normal range at 22.2 mg/dl at 3-month follow-up and normalized at 6-month follow up. Again, normal anion gap and no symptoms of lactic acidosis therefore not felt to be clinically related to the device.

3) P.N.- 10.6 mg/dl starting level, increased level, 19.0mg/dl, at 3 months but still within the normal range for that laboratory (5-20 mg/dl).

4) K.T.- Baseline 10 mg/dl (4-16 mg/dl) increase to 18mg/dl, which is slightly above normal for this laboratory, at 3-month follow-up. The patient had no symptoms and a normal anion gap making this increase not clinically relevant.

5) A.D.- Patient had an elevated level of 16 mg/dl (5-15mg/dl) at the start of the study. He was able to enroll because he had a normal anion gap and no clinical symptoms of Lactic Acidosis. His lactate rose slightly to 19mg/dl at his 3-month follow up.

Of equal or greater clinical significance, nine patients experienced a decrease in their serum venous lactate levels over the course of the study. All of these patients had an elevated lactate level at baseline but had normal anion gaps and no symptoms of lactic acidosis and therefore were allowed to enroll in the study. Seven of the nine, in fact, had a normalization of their lactate levels as the study progressed.

8.4   DEATHS, DISCONTINUATIONS DUE TO ADVERSE EVENTS, AND OTHER SERIOUS ADVERSE EVENTS

8.4.1   Deaths

No deaths have occurred during the study.

8.4.2   Discontinuations Due to Adverse Events

No patients have discontinued the study due to an adverse event.

8.4.3   Other Serious Adverse Events (If Applicable)

No serious adverse events have been reported in the study.

8.5   LABORATORY EVALUATIONS

Laboratory evaluations of serum chemistries, including liver function tests (LFTs), serum bicarbonate levels, serum lactate, PT/PTT, and CBC with differential are taken at patient screening (Day 1) and again every 3 months during treatment and at 6 and 12-month follow-up appointments following the final treatment.

Serum venous lactate levels are difficult to obtain as they must be done without a tourniquet and placed on ice and delivered to the laboratory stat. The serum lactate levels obtained to date have been wide ranging. Nine patients experienced a decrease in lactate level and five patients experienced an increase in lactate levels. Of note, none of the changes were accompanied by any abnormal anion gap or clinical symptoms of lactic acidosis. The decreases all occurred in patients with baseline elevated venous lactate levels and clinically one would expect a further worsening of these levels if repeated exposure to this device caused a significant change in venous lactate levels.

Three patients did have isolated increases in blood glucose but none of these were felt to be clinically relevant or related to the device. Minor fluctuations in liver function tests were common but again not clinically relevant or felt to be related to the device. One patient, as previously noted, has a history of chronic passive Hepatitis B. His liver enzymes remained normal through out the study to date.

9. INTERIM CONCLUSION

Based on patients treated to date, the overall impression is that New-Fill® is extremely well tolerated and acceptable to patients. Overall, patients experienced an increase in confidence and an improved self-image. It has a very favorable safety profile with no severe adverse events reported to date. Expected events of swelling and possible bruising were well tolerated by patients in that all patients would recommend this treatment to a friend. Small nodules (<3mm) have occurred in 9.2% of patients with the majority resolving by 6 months. To date, at 6-month follow-up, it appears to be an extremely safe and effective treatment for HIV-Associated Lipoatrophy.

SAFETY, EFFICACY AND IMPACT OF INTRADERMAL NEW-FILL® IMPLANTS IN PERSONS WITH HIV-ASSOCIATED LIPODYSTROPHY

A SINGLE SITE, OPEN LABEL STUDY
Protocol Number 3
April 2002

Principal Investigator
Co-Investigator

(office)
(fax)

Study Monitor

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CONTENTS

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STUDY SUMMARY

The goal of the study is to evaluate the long-term safety and efficacy of the medical device New-Fill® (Polylactic Acid, Poly-L-Lactic acid, PLA) in the treatment of facial HIV-Associated Lipodystrophy as well as the effect of this treatment on patient's overall sense of well being.

All patients participating in the study will have clinically significant HIV-Associated Lipodystrophy. The pattern of facial wasting may involve fat loss of the cheeks and or temples, however only cheek skin thickness response to therapy will be measured.

1-OBJECTIVES

1.1 Primary Objective
To evaluate the quantifiable improvement in facial wasting after serial intradermal injections of New-Fill®

1.2 Secondary Objectives
   a. To evaluate the safety of New-Fill® usage in repeated treatments in patients with HIV/AIDS
   b. To evaluate the long term (greater than 6 months) durability of the increased skin thickness
   c. To evaluate the immediate and long term patient acceptance of serial treatments of New-Fill®
   d. To evaluate the psychological impact of treatment of HIV-Associated Lipodystrophy with New-Fill® intradermal injections.

2-METHODOLOGY

This study is a single site, open label design. Patients will act as their own controls. The duration of follow up will be 12 months after the last treatment session.

3-ELIGIBILITY CRITERIA

3.1 Inclusion Criteria
   Age >18
   Lipodystrophy of the cheek/temple of a degree that is bothersome to the patient i.e. clinically significant
   Willingness to participate actively in the study
   HIV seropositivity

3.2 Exclusion Criteria
   Facial injections with any substance within the last 3 months
   Active infection of the face
   Active cutaneous Kaposi Sarcoma involving the treatment area
   Active treatment with interferon or systemic corticosteroids
   Pregnancy or Breast Feeding
   Non-compliance based on history or previous experience
   Signs or symptoms of lactic acidosis
   Known pre-existing renal disease
   Poorly controlled Diabetes Mellitus

3

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4-STUDY SCHEMA

Patient presents with clinically significant facial wasting desiring correction, willing to participate in the study as evidenced by signed, written informed consent.

Intradermal New-Fill® Injections: The patient will receive intradermal injections of New-Fill® into the targeted treatment areas, using 1ml to 6 ml of reconstituted New-Fill®(50mg of Polylactic acid per ml) per session. A typical treatment session involves 6 mls of the device. Sessions will be 3 weeks apart with an allowable variability of 10 days. Patients will receive a minimum of 1 and a maximum of 6 treatment sessions as mutually agreed is necessary by the injecting physician and the patient.

Skin Thickness Measurement: Each subject will have baseline caliper skin thickness determined at bilateral fixed points (see diagram Appendix E) located at the intersection of the vertical axis through the lateral canthus of the eye and the horizontal axis of the nares. Caliper skin thickness will be determined prior to subsequent treatments, at 6 months and 12 months following the final treatment session.

Psychological Well Being Questionnaire: Patients will complete initial questionnaires ascertaining patient feelings regarding overall health, emotional well being and effects of HIV-Associated Lipodystrophy. Patients will complete the same questionnaire at the end of treatment and 12 months after the final treatment. Patients will act as their own control regarding validity of the study questionnaire. Sample Questionnaire is shown in Appendix C.

Serial Digital Photography: Each patient will be photographed in the sitting position using an AP and lateral oblique technique at a distance of three feet. Photographs will be taken prior to the first session and before each subsequent treatment session. Additional photographs will be taken at 6 and 12 months after the final treatment session and in the event of any adverse event.

Laboratory Studies: Initial laboratory studies will include serum chemistries, Liver function tests (LFT's) serum bicarbonate, serum lactate, PT/PTT and CBC with differential. Lab studies will be repeated every three months during treatment and at 6 and 12 month follow up appointments following the final treatment.

Study Questionnaire: Each patient will complete a questionnaire regarding acceptability of treatment at each treatment session. Patients will also complete questionnaires at the end of treatment and at 6 and 12 months following final treatment to determine overall satisfaction and perceived durability of the device. Investigators will also complete evaluation forms at each treatment session and at 6 and 12 month follow up visits. Sample forms are included in Appendix D

5-STUDY ENDPOINTS

5.1 Primary Endpoint
Evaluation of the percent change in overall skin thickness as evidenced by skin caliper measurement following serial treatment sessions as well as 12 month durability of the change.

5.2 Secondary Endpoints
Summarize demonstrable effects of intradermal injections on facial defects as evidenced by patient satisfaction and serial photography.
Summarize effects of treatment on patient's psychological well being.
Summarize acceptability and tolerability of treatment as reported by patients.
Summarize safety of treatment as reported by adverse events and any significant change in lab values over the course of the study period.

4

6-DURATION OF STUDY

24 Months

7-SAMPLE SIZE

The study will be limited to 100 subjects.

8-START OF STUDY

Projected start date July 2002

9-INTRODUCTION AND RATIONALE

Facial Lipodystrophy has many known and also several hypothetical causes. Initially thought to be a side effect of the class of medications known as protease inhibitors, it is now felt to be multifactorial including HIV itself, HIV antiretrovirals and the aging process itself.(1,2,3,4,5) Regardless of the actual cause, the affect of facial wasting on patient's overall mental health can be significant.(6) In addition, as HIV/AIDS patients are living longer with the advances in medicine, the problem of how to effectively treat HIV-Associated Lipodystrophy has become more critical.

Multiple approaches have been attempted to address this problem. Some of these treatments are approved for use in this country while others are offered in foreign countries in sometimes unregulated settings.

Biodegradable Implants: These can be broadly put in two categories: animal origin and human origin. The oldest of these is Bovine collagen. Although this product has the longest clinical usage, it carries a 2%-3% incidence of allergic reaction due to the foreign protein content. In addition, the amount needed for correction of facial wasting is significant, rather costly and the resorption of the material is particularly rapid on the order of several weeks to months (7,8) and offers no permanent filling effect. Hyaluranate gels have a very rapid absorption by the body that limits their cosmetic usage. (9) More recently, collagen implants of human origin (Cymetra™, Fascian™) have become available. Results with these products have been disappointing.

Non-biodegradable synthetic implants; including silicone oil and Polymethylmethacrylate (PMMA) beads. Silicone has the problem of inflammatory granuloma formation, sometimes years after insertion as well as the chance of migration of product. (10) PMMA is placed in a bovine collagen solution which carries the chance of allergic reaction. (11,12) Non-biodegradable implants do not allow for the possibility of cosmetic adjustments after insertion afforded by biodegradable implants.

Fat cell transfer/transplant: In addition to the technical difficulties in harvesting sometimes limited fat in HIV patients, the re-implanted tissue tends to disappear at the same rate as the original fat loss due to lipoatrophy. (13)

New-Fill®, polylactic acid hydrogel (PLA) is a synthetic polymer which is biodegradable, biocompatible and immunologically inactive (14). As a synthetic polymer, PLA contains no product of animal origin which rules out any risk of viral or prion contamination. Past research has shown PLA to be well tolerated in HIV patients (15). PLA has a long track record of use in a variety of medical applications such as resorbable suture material used in neurologic, ophthalmologic and abdominal surgeries. (16) Fixation devices have been created for ligament and bony repair (17,18,19,20) utilizing the PLA molecule. PLA has been used as the vector for sustained release of medication administered orally and parenterally (subcutaneous, intramuscular). The temporary entrapment of the drug within a bioabsorbable polymer matrix ensures that the active substance is protected and gradually released in a controlled manner as the polymer hydrolyzes (21,22,23,24,25). PLA is widely used outside the USA for a variety of

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9-INTRODUCTION AND RATIONALE (cont'd)

aesthetic procedures such as treatment of facial rhytides. Ongoing studies are being conducted to evaluate the long-term durability of PLA in facial aesthetics (26)

New-Fill® has a dual mechanism of action. There is an immediate mechanical action that is related to the volume of hydrogel injected. This effect is transitory and gives way to the formation of new collagen induced by the properties inherent in polylactic acid. This neocollagenosis is due to the appearance of a fibrous dermal layer in reaction to the presence of the implant (27). This new collagen persists despite the resorption of the PLA implant. It is this neocollagenosis that gives New-Fill® the possibility of long-term correction of facial wasting with the safety·inherent in bioabsorbable materials.

The evaluation of New-Fill® to correct HIV-Associated Lipodystrophy is underway in an international, multicenter study. (28) Preliminary results are encouraging and adverse events rare (15, 28). New-Fill® has been used in this country under compassionate usage guidelines for persons with HIV disease with equally promising results. (29). Of note, the investigators of this study were some of the first physicians to use New-Fill® in the treatment of HIV-Associated Lipodystrophy under a program organized by DAAIR, an HIV buyers co-op located in New York, which was able to expedite import into this country for personal usage from June to October 2001. This usage has now been restricted to those patients currently under treatment. Our experience has also been extremely favorable with no serious adverse effects reported.

10-SUBJECT SCREENING

Screening evaluations will occur on Day 1 and consist of the following:

Clinical evaluation by the study investigators, including history and limited physical examination

Laboratory evaluation of serum chemistries including liver function tests (LFT's), serum bicarbonate, serum lactate, PT/PTT and CBC with differntial.

Study process and procedures including Consent Form explanation and witnessed consent

Facial Digital Photography

Initial Caliper skin thickness measurement

Baseline Psychological Well Being questionnaire

Pretreatment questionnaire

In the case of pre-menopausal female study patient, serum pregnancy test with negative result documented prior to any treatment. In addition, the importance of not becoming pregnant during the study period will be emphasized to the patient.

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11-TREATMENT AND MONITORING

Each treatment will be provided by one of the two study investigators: injection at multiple sites and depths with a total of 1ml to 6 ml of New-Fill® to the marked treatment area. Volume of New-Fill® injected at each treatment session will be subjective and individualized to produce the desired filling effect for that patient based on the investigators previous experience. No more than 6 ml of reconstituted New-Fill® will be used at anyone treatment session. Reconstitution of New-Fill® will be according to manufacturer recommendations.

Treatment sessions will be 3 weeks apart with a maximum deviation of 10 days to a maximum total of 6 treatment sessions in a single patient during the study period.

Treatment will be stopped in the case of local skin reaction, infection, patient intolerance, significant and unexplained changes in lab values and on request of the patient.

Caliper skin thickness measurements will be performed prior to each treatment, after the final treatment and 6 and 12 months after final treatment.

Patient questionnaires will be administered at each treatment session and at 6 and 12 months after final treatment. Patients will be contacted by phone within 48-72 hours after each treatment to monitor for any adverse effects.

Digital photography of treatment areas will be performed prior to each treatment session, after final treatment and 6 and 12 months after the final treatment. Additional photos will be taken in the event of an adverse event.

12-ETHICAL CONSIDERATIONS

12.1 Data Collection
Monitoring will be performed by the Principal Investigator and study monitor at the study site.

12.2 Study Site
The only designated study site will be ███████████████████████

12.3 Confidentiality
The study material and case records will be stored in a secure, locked location accessible only to the persons involved in the conduct of this study.

12.4 Regulatory Issues
The study will be conducted using the consent procedures as detailed by the ████████████
████████████

12.5 Emergency Medical Services
A physician licensed to practice medicine in the ██████████ will be on call and available 24 hours per day for study participants ████████████ r is located 5 miles from the study center and is available 24 hours per day for emergency services.

13 DATA COLLECTION

At the completion of the study, change in caliper skin thickness will be analyzed for statistical significance. Psychological Well Being questionnaire data will be compared and significant trends identified regarding the impact of treatment on patients overall well being. Patient questionnaire data will be tabulated and summarized by the study personnel. Photographic images of subject progression will be made available to interested parties after the study period provided that subject consent has been obtained for their distribution.

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14 REFERENCES

1. Chene G, Angelini E, Cotte L, Lang JM, Morlat P et al. *Role of long-term nucleoside-analogue therapy in Lipodystrophy and metabolic disorders in human immunodeficiency virus-infected patients.* Clin Infect Dis 2002 Mar 1:34(5):649-57.
2. Nolan D, John M, Mallal S. *Antiretroviral therapy and the Lipodystrophy syndrome, part2: concepts in aetiopathogenesis.* Antivir Ther 2001 Sep;6(3):145-160.
3. Carr A, Samaras K, Chisholm J, Cooper DA. *Pathogenesis of HIV-1 protease inhibitor-associated peripheral Lipodystrophy, hyperlipidemia, and insulin resistance.* Lancet 1998, 351:1881-83.
4. Holstein A, Plaschke A, Egberts EH. *Lipodystrophy and metabolic disorders as complications of antiretroviral therapy of HIV infection.* Exp Clin Endocrinol Diabetes 2001;109(8):389-92.
5. Boufassa F, Dulioust A et al. *Lipodystrophy and metabolic disorders in 646 HIV-1 infected patients previously treated with or without protease inhibitors.* 7th Conference on Retrovirus and Opportunistic Infections.
6. Martinez E, Ruiz M, Garcia-Viejoio MA. *Strategies for treating HIV-related Lipodystrophy.* Expert Opin Investig Drugs 2001 Aug;10(8):1443-56.
7. Pons-Guiraud A. *Reactions of delayed hypersensitivity with implants of bovine collagen. A study of 810 patients.* Nouv Dermatol 1992, 11:422-432.
8. Stegman SJ, Chu S, et al. *A light and electron microscopic evaluation of Zyderm collagen and Zyplast collagen implants in aging human facial skin.* Arch Dermatol 1997, 123:1644-1649.
9. Ghersetich I, Teofoli P, et al. *Ultrastructural study of hyaluronic acid before and after the use of pulsed electromagnetic field, electrorydesis, in the treatment of wrinkles.* Int J Dermatol 1984, 33:661-663.
10. Faure M. *Complications from silicone implants and other inert materials.* Ann Dermatol Venerol 1995, 122:455-459.
11. Lemperle G, Ott H, Charrier U et al. *PMMA microspheres for intradermal implantation. Part I: Animal research.* Ann Plast Surg 1991, 26(1):57-63.
12. Lemperle G, Hazan-Gauthier N, Lemperle M. *PMMA microspheres (Artecoll) for skin and soft tissue augmentation. Part II clinical investigations.* Plast Reconstr Surgery 1995, 96:627-634.
13. Wechselberger G, Sarcletti M, Meirer R, Bauer T, Schoeller T. *Dermis-Fat Graft for Facial Lipodystrophy in HIV-Positive Patients: Is it worthwhile?* Ann Plast Surg2001Jul; 47(1):99-100.
14. Chadrashekar G, Udupa N, et al. *Biodegradable injectable implant systems for long-term drug delivery using poly lactic-co-glycolic) acid polymers.* J Pharm Pharmaco 1996, 48:669-674.
15. Armard P, Saint-Marc T, Katz P. *The effects of polylactic acid (New-Fill®) as therapy for Lipoatrophy of the face Abstract.* 2nd International Workshop of Adverse Drug Reactions and Lipodystrophy in HIV, Toronto Canada. Sept 2000.
16. Kronenthal RL. *Biodegradable Polymers in medicine and surgery.* Poly Sci Technol. 1975, 8:120-137.
17. McGuire DA, Barber FA, Elrod BF, Paulos LE. *Bioabsorbable interference screws for graft fixation in anterior cruciate ligament reconstruction.* Arthroscopy 1999, Jul-Aug:15(5):463-73.
18. Jones HP, Lemos MJ, Wilk RM, Smiley PM, Gutierrez R, Schepsis AA. *Two year follow up of meniscal repair using a bioabsorbable arrow.* Arthroscopy 2002, Jan;18(1):64-69.
19. Balch OK, Collier MA, DeBault LE, Johnson LL. *Bioabsorbable suture anchors(co-polymer 85/15 D,L lactide/glycolide) implanted in bone: correlation of physical/mechanical properties, magnetic resonance imaging and histological response.* Arthroscopy 1999, Oct;15(7):691-708.
20. Barca F, Busa R. *Austin/chevron osteotomy fixed with bioabsorbable poly-L-lactic acid single screw.* J Foot Ankle Surg 1997, Jan-Feb;36(1):15-20.
21. Morris W, Steinhoof MC, Russel PK. *Potential of polymer microencapsulation technology for vaccine innovation.* Vaccine 1994, 12:5-11.
22. Rolland A, Wagner N, Chatelus A, Shroot B, Schaefer H. *Site-specific drug delivery to pilosebaceous structures using polymeric microspheres.* Pharm Res 1993, 10:1738-1744.
23. Conn RE, Kolstad JJ, Borzelleca JF, Dixier DS, Filer LJ, et al. *Safety assessment of polylactide(PLA) for use as a food-contact polymer.* Food Chem Toxicol 1995, 33:273-283.
24. Shively ML, Coonts BA, Renner WD, Southard JL, Bennet AT. *Physico-chemical characterization of a polymeric injectable implant delivery system.* J Control Release 1995, 33:237-243.
25. Fournier C, Hecquet B, Bouffard P, Vert M, Caty A, et al. *Experimental studies and preliminary clinical trial of vinorelbine-loaded polymeric bioresorbable implants for the local treatment of solid tumors.* Cancer Res 1991, 51:5384-91.

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14-REFERENCES (cont'd)

26. Jacquet A, Moore N. *Evaluation of the Acceptability, Innocuity, and Performance of a gel made of Microspheres of Polylactic Acid- New-Fill® for the Injection of Vertical Facial Wrinkles in Women.* Essais Cliniques Cosmetologie, Department de Pharmacologie, Universite Victor Segalen Bordeaux 2, Bordeaux, France. March 2001
27. Gogolewski S, Jovanovic M, Perren SM, Dillon JG, Hughes MK. *Tissue response and vivo degradation of selected polyhydroxyacids: (PLA, PHB, PHB/VA).* Journal Bio Mat Research 1993, 127:1135-1148
28. Katlama C, Johnson M, et al. *Study of the Safety and Efficacy of Intradermal cheek implants of Polylactic Acid in HIV Seropositive Patients with severe facial wasting.* Study in progress, Sponsor: Hopital Pitie-Salpetriere, 47-83 Blvd de Hopital, 75013 Paris, France.
29. Engelhard P. Compassionate use of Facial Intradermal implants of New-Fill® in Persons with HIV-Associated Lipoatrophy of the Face. Study in progress.

15-STUDY MEDICATION

New-Fill® will be purchased for the study through the Manufacturer and their North American Distributor by the Sponsor, ███████████████████. The address of the manufacturer is: Biotech Industry, SA, 21 Rue Bernard HAAL, L 1711 Luxembourg. Telephone 352-26-25-94-62, Fax 352-26-25-94-60, web site www.new-fill.com. The Scientific Director of Biotech is ███████████. The distributor of New-Fill® is Farmaceuticos BIO-PLA de Mexico SA, Paseo de la Reforma No 509 11-D, Mexico 06500, DF. Telephone 525-211-15-11, fax 525-286-45-52, web site www.newfill-mexico.com . The Director of Farmaceuticos BIO-PLA is ███ ███████.

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APPENDIX A

■■■■■■■■■

Principal Investigator Name: _____

■■■■ otocol #: _____

Sponsor Protocol #: _____

Sponsor: _____

Study Drug/Device: _____

Indication for Use: _____

Subject ID: _____
(Initials/Number)

Subject Age: _____ ☐ Male ☐ Female

DATES

This report: _____
(MM/DD/YYYY)

☐ Initial ☐ Follow-up

First Dose/Use: _____
(MM/DD/YYYY)

SAE Onset: _____
(MM/DD/YYYY)

SAE Description / Treatment / Outcome:

☐ Resolved   ☐ On-Going

Pertinent Subject History:

Seriousness *(Check all that apply):*
☐ Death
☐ Life Threatening
☐ Hospitalization *(Initial or Prolonged)*
☐ Disability/Incapacity
☐ Other *(Specify)* _____

Relationship to Drug / Device:
☐ Not Related
☐ Possibly   ☐ Probably
☐ Definitely Related
☐ Unknown

Do you recommend changes to the protocol?   ☐ No ☐ Yes; if yes, attach proposal
Do you recommend changes to the consent form? ☐ No ☐ Yes; if yes, attach proposal

Below this line for WIRB use only

Reviewed by: _____	*Date:* _____
Comment: _____	
Reported to Board by: _____	*Date:* _____ *Action:* _____

AE report 053001

020199001

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		Lab Results													Skin Thickness(mm)		Photos Taken	Questionnaires Completed (Y/N)		
Tx #	Date	Na	K+	Cl	HCO3	Anion Gap Na-(Cl+H CO3)	BUN	Cr	Glucose	Lactate	AST	ALT	CBC	PT/PTT	Right	Left	(Y / N)	Well Being	Patient	MD
0															/					
1		X	X	X	X	XXXXXXX	X	X	X	X	X	X	X	X	/	XXXXXXXXX	X	X		
2		X	X	X	X	XXXXXXX	X	X	X	X	X	X	X	X	/			X		
3		X	X	X	X	XXXXXXX	X	X	X	X	X	X	X	X	/			X		
4															/			X		
5		X	X	X	X	XXXXXXX	X	X	X	X	X	X	X		/			X		
6		X	X	X	X	XXXXXXX	X	X	X	X	X	X	X		/				X	
6 Mnth Post																				X
12 Mnth Post																				X

COMMENTS:

Pt #_____   Date_____

Psychological Well Being Questionnaire

Please circle the answer closest to your feelings regarding the following:

1) I am glad to be alive:

1	2	3	4	5
strongly agree	somewhat agree	neutral	somewhat disagree	strongly disagree

2) In general, I am happy with my life:

1	2	3	4	5
strongly agree	somewhat agree	neutral	somewhat disagree	strongly disagree

3) My facial appearance makes me sad at times:

1	2	3	4	5
strongly disagree	somewhat disagree	neutral	somewhat agree	strongly agree

4) I feel my overall health is good:

1	2	3	4	5
strongly agree	somewhat agree	neutral	somewhat disagree	strongly disagree

5) My facial appearance reflects the state of my overall health:

1	2	3	4	5
strongly agree	somewhat agree	neutral	somewhat disagree	strongly disagree

6) My facial appearance affects my social interactions with others:

1	2	3	4	5
Never	seldom	sometimes	often	daily

APPENDIX D

Use of New-Fill®   Protocol #3   PT ID#_____

TO BE COMPLETED BY PATIENT

First Treatment Session   Date_____

Age_____ Sex_____   # of years with HIV_____ #of years on Anti-virals_____

Current Medications_____

Allergies_____

Areas affected by lipodystrophy: Cheeks_____ Temples_____ Both_____

Immediately After First Treatment
Pain/Discomfort of Treatment: 1= Mild
                                     5= Severe _____

Three Weeks After First Treatment   Date_____

Side Effects_____

_____

Treatment #_____   Date_____

Side Effects_____

_____

Satisfaction with Treatment Outcome: 1=Dissatisfied
                    5=Very Satisfied_____
Treatment #_____   Date_____

Side Effects_____

_____

Satisfaction with Treatment Outcome: 1=Dissatisfied
                    5=Very Satisfied_____
Treatment #_____   Date_____

Side Effects_____

_____

Satisfaction with Treatment Outcome: 1=Dissatisfied
                    5=Very Satisfied_____
Treatment #_____   Date_____

Side Effects_____

_____

Satisfaction with Treatment Outcome: 1=Dissatisfied
                    5=Very Satisfied_____

Study Doctor_____   Date_____

Use of New-Fill®   **Protocol #3**   **PT ID#_____**

<u>**Six Months After Treatment Series**</u>   **Date_____**

Side Effects_____
_____

            Satisfaction with Treatment Outcome: 1=Dissatisfied
                    5=Very Satisfied_____

Would you recommend this treatment to a friend?   YES_____ NO_____

Twelve Months After Treatment Series   **Date_____**

Side Effects_____
_____

            Satisfaction with Treatment Outcome: 1=Dissatisfied
                    5=Very Satisfied_____

Would you recommend this treatment to a friend?   YES_____ NO_____

Study Doctor_____   Date_____

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TO BE COMPLETED BY DOCTOR

First Treatment Session   Date_____

- *Investigator Rating of Lipodystrophy: mild   moderate   severe   (circle one)*
Baseline Skin Thickness Right_____mm Left_____mm

Treatment #_____   Date_____

Pre-treatment Skin Thickness Right_____mm   Left_____mm

Treatment #_____   Date_____

Pre-treatment Skin Thickness Right_____mm   Left_____mm

Treatment #_____   Date_____

Pre-treatment Skin Thickness Right_____mm   Left_____mm

Treatment #_____   Date_____

Pre-treatment Skin Thickness Right_____mm   Left_____mm

Treatment Series Completion
Date_____

- *Investigator Satisfaction with Outcome: 1=Dissatisfied*
                              *5=Very Satisfied*_____

Skin Thickness Right_____mm Left_____mm

Six Months After Treatment Series   Date_____

- *Investigator Satisfaction with Outcome: 1=Dissatisfied*
                              *5=Very Satisfied*_____

Skin Thickness Right_____mm Left_____mm

Twelve Months After Treatment Series   Date_____

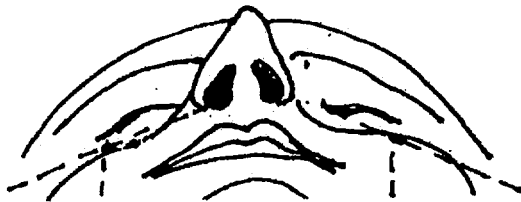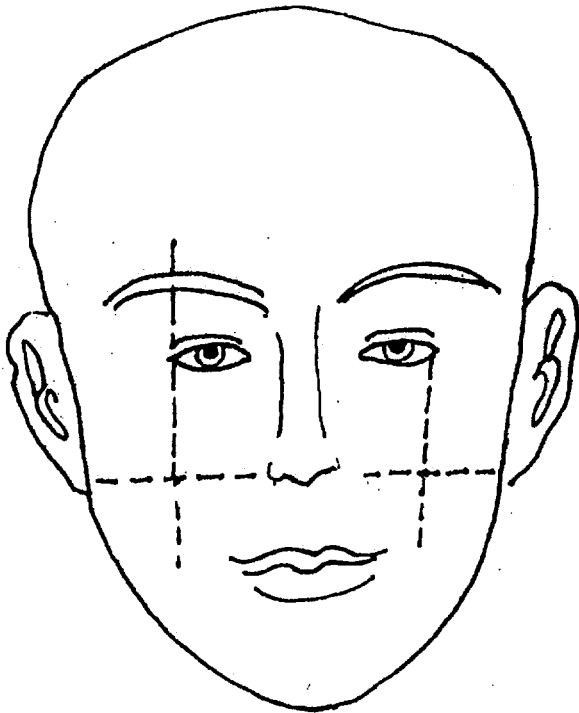- *Investigator Satisfaction with Outcome: 1=Dissatisfied*
                              *5=Very Satisfied*_____

Skin Thickness Right_____mm Left_____mm

Study Doctor_____   Date_____

Clinical Appendix

Appendix 12.2.9

Safety Report on Post-marketing Spontaneous Adverse Event Reports for NEW-FILL®

POST-MARKETING SPONTANEOUS ADVERSE EVENT REPORT APPROVAL

Title : New-Fill® Post Marketing Safety Report

Circulated Version: Final 1.0

You will find attached for formal approval the above referenced report:

Please sign below and return this document at your earliest convenience.

Author(s)		
	Signature:	Date : 10-27-03

preprint name:	Signature:	Date : 10/27/03

preprint name:	Signature:	Date : 10/30/03

preprint name:	Signature:	Date : 31 Oct 2003
	First Last	

Safety report on post-marketing spontaneous adverse event reports for New-Fill®

(Skin implant)
CE mark provided by G-MED (0459)

Period November 25, 1999 – July 31, 2003
Report Version: Final

Summary

Three serious spontaneous adverse events were reported for New-Fill® from November 1999 through July 2003. The serious adverse events included one report each of abscess at injection site, allergic reaction, and injection site granuloma.

In summary, post-marketing spontaneous adverse events associated with New-Fill® treatment are uncommon. In almost all cases, these consist of localized injection site events that are considered in the vast majority of situations to be due to injection technique.

Poly-L-Lactic Acid, Injectable
Post-Marketing Spontaneous Adverse Event Report

Content

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1. Introduction

Sculptra is marketed in the following countries as New-Fill®: Argentina, Australia, Brazil, Bulgaria, European Union countries (Austria, Belgium/Luxembourg/Netherlands, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Portugal, Spain, Sweden, United Kingdom), Hungary, Israel, Lebanon, Malaysia, Mexico, Morocco, Norway, Poland, Romania, Russia, Saudi Arabia, South Africa, Switzerland, and the United Arab Emirates.

New-Fill® is approved for marketing use in Europe as a Class III device labelled for the following indication:

"New-Fill® is suitable for increasing the volume of depressed areas, particularly to correct skin depression, such as in skin creases, wrinkles, folds, scars and eye rings. It is particularly useful for degenerative skin lesions due to skin aging."

The English portion of the EU label is provided in Section 6.

A CE mark for New-Fill® was granted by the French Notified Body G-MED (Groupement pour l'evaluation des Dispositifs Médicaux – Department of Evaluation of Medical Devices) on November 25, 1999, providing marketing approval in all participating EU nations.
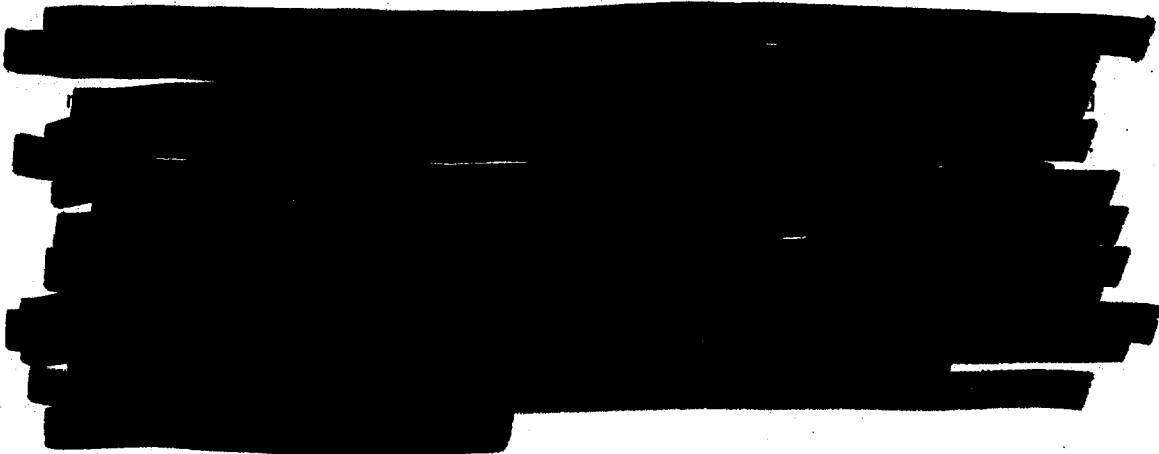
2. New-Fill®

New-Fill®, as marketed, consists of lyophilised product, in a glass vial, along with directions for use. The lyophilisate is reconstituted with sterile water. The composition of the lyophilisate within the glass vial is:

Composition per vial	Mass (mg)	% w/w
Poly-L-lactic acid (PLLA)		
Sodium carboxymethylcellulose (Carmellose)		
Non-pyrogenic mannitol		
TOTAL		

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Poly-L-lactic acid (PLLA) provides the durable tissue-filling effect.

3. Safety Data

3.1 Introduction

3.2 Summary of

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3.6 Demographics

The majority of the patients reported to have experienced adverse events were in the 40-65 years age range, with occasional younger patients. Age was not reported for a significant proportion of patients.

The number of case reports for females exceeds that for males, although gender was not specified in a large proportion of reports.

No data are available on race.

3.7 Other information on use of New-Fill®

The site of injection and underlying reason for treatment were not specified in the vast majority of spontaneous reports. Moreover, the reasons for and sites of treatment might not have been complete, having only been mentioned if adverse events occurred in that region. In general, it can be stated that injections in patients for whom spontaneous adverse events were reported had almost always been performed in various areas of the face, including the nasolabial folds, peri-orbital area, peri-oral area, lips, and cheeks.

Most patients received repeated treatments over a period of several months. The dose (volume and concentration) per treatment, type of diluent, or the total dose received was reported for very few spontaneous adverse event reports.

Information on concomitant treatment or treatment with other cosmetic products before New-Fill, such as botulinum-toxin (botox), hyaluronic acid, and/or collagen is also available in only a very few cases.

3.8 Treatment of adverse events

Details of any treatment of adverse events are often not provided in spontaneous adverse event reports. Treatment for the most common type of spontaneous adverse event, injection site nodule, was reviewed. The most commonly used treatments were corticosteroids injected into nodule(s), topical corticosteroids, 5 FU injected into nodule(s), systemic antibiotics (usually tetracyclines), and oral corticosteroids.

In most cases long-term followup or outcome is not available. However, some patients have experienced spontaneous diminution of nodules or have experienced improvement after one or more of the above treatments.

4. Discussion

The most common type of spontaneous adverse event reported was "injection site nodule". The formation of nodules during the first 6 months after treatment is considered to be most likely due to a too superficial injection of New-Fill®. Nodules occurring later after initial treatment may be due to injection of New-Fill® at inappropriate sites (lips) and/or with inappropriate technique such as over-correction.

Only three serious spontaneous adverse events, injection site abscess, allergic reaction, and injection site granuloma, were reported worldwide over this time period.

Most reports provided limited information regarding the concomitant use of other medicinal products or treatments with New-Fill®. Volumes injected, doses, and dilutions of New-Fill® are also generally not available. There is no evidence that gender or age factors predispose patients to adverse events, although post-marketing spontaneous reports do not provide an adequate setting to evaluate these issues.

5. Conclusion

Post-marketing spontaneous adverse events associated with New-Fill® treatment are uncommon. In almost all cases, these consist of localized injection site events that are considered in the vast majority of situations to be due to injection technique.

6. New-Fill European Package Insert

(Please note: BioTech is the original owner of the product. A revised Package Insert for Europe has been submitted to G-MED and is under review.)

NEW-FILL®
Skin Implant

RECONSTITUTION
NEW FILL® is reconstituted extemporaneously in the following way:
1. Remove the flip-off capsule from the vial.
2. Take a sterile single-use 3ml or 5ml syringe (graduated in 1/10ml) and a 18 1/2 G sterile needle and attach the needle to the syringe.
3. Remove 3ml of sterile water for injections (water for injections: European Pharmacopea third edition, monograph 0169) with the syringe.
4. Slowly add the 3ml of water to the dry powder, by introducing the 18 1/2 G needle into the rubber bung of the vial.
5. Let it stand for at least 20 minutes (do not shake it) to ensure that the powder dissolves in the water for injections.
6. Shake until a homogeneous translucid suspension is obtained. It is ready for use.
7. Take 0.45X12 (26G) needles, depending on the indication, to inject intradermally.

Medical Instructions
NEW FILL® is a skin implant in the form of a sterile apyrogenic suspension, which is reconstituted from a sterile dry powder by the addition of water for injections (European Pharacopea third edition, monograph 0169). This suspension contains microspheres of Poly-L-Lactic Acid, the crystalline form of P.L.A. It is a synthetic polymer, is biocompatible, biodegradable, immunologically inert, free from toxicity, comes from the alpha-hydroxy-acid family and its resorption is complete and controlled.

PRESENTATION
The NEW FILL® dry powder is supplied in an elongated white glass vial with an aluminium ring at one end, which is hermetically sealed by a rubber bung, covered by a flip-off capsule.
The contents of each vial is reconstituted with 3 ml of sterile water for injections, which is enough for three 1 ml NEW FILL® syringes.

COMPOSITION OF THE DRY POWDER
Each vial contains
Poly-L-Lactic Acid......................0.150 g
Sodium Carmellose.......................0.090 g
Apyrogenic Mannitol....................0.1275 g
COMPOSITION OF NEW FILL®
Dry powder..............................0.3675 g
Sterile water for injections..................3 ml

MODE OF ACTION
NEW FILL® is implanted by subcutaneous or intradermal injection. The tight granulometric distribution of the microspheres of Poly-L-Lactic Acid, its slow degradation kinetics, and a

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Poly-L-Lactic Acid, Injectable
Post-Marketing Spontaneous Adverse Event Report

viscosity which is suitable for subcutaneous injections, gives **NEW FILL®** its mechanical properties and prolonged resorbability, which make this implant suitable for filling areas of depressed skin.

INSTRUCTIONS FOR USE

NEW FILL® is suitable for increasing the volume of depressed areas, particularly to correct skin depression, such as in skin creases, wrinkles, folds, scars and eye rings. It is particularly useful for degenerative skin lesions due to skin aging.

Injection technique: the depth of injection and quantity of **NEW FILL®** used depends on the area to be treated and the result expected.

Over-corrections should be avoided, but if they occur, the area concerned should be massaged using light pressure.

Once the required amount of filling is reached, the slow resorption of **NEW FILL®** means that further injections to the same area are not necessary for some time.

CONTRA-INDICATIONS

Do not use in the case of acute or chronic skin disease (infection or inflammation) near the area to be treated.

WARNING

NEW FILL® should only be used subcutaneously or intradermally.
Do not resterilise the vial.
Do not inject into a blood vessel, to avoid the risk of skin infarction or embolism of a blood vessel. The fluidity of **NEW FILL®** makes it easy to aspirate with the syringe before injection, to ensure that the needle is not in a blood vessel.
Over-correction should be avoided, especially in the peri-orbital area.
Only mix the powder with sterile water for injections (water for injections: European Pharmacopea third edition, monograph 0169).
Use the needles supplied for this use and the single-use sterile syringes.

PRECAUTIONS FOR USE

The following precautions should be observed:
The injection site should be cleaned and free from inflammation or infection.
As with all injections, patients treated with anti-coagulants may run the risk of a haematoma or localized bleeding at the injection site.
NEW FILL® has not been proved to be harmless for pregnant women or children.
No studies of interactions of **NEW FILL®** with drugs or other substances or implants have been made.

SIDE EFFECTS OF THE TREATMENT

The side effects usually resulting from the injections are bleeding from an area the size of the point of the needle, which disappears as soon as the injection is finished, or localized redness at the injection site, haematomas or even slight oedema, which disappear within 24 to 48 hours in most cases, or in 4 to 6 days for the lip mucosa. Normal very superficial whitening may occur during injection, but disappears spontaneously.
Exceptionally, an invisible nodule may be palpable in the dermis, which is due to over-correction, and disappears completely in a few months.

ANY SIDE EFFECTS SHOULD BE NOTIFIED TO THE CORRESPONDING ADDRESS:
In Europe:

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Poly-L-Lactic Acid, Injectable
Post-Marketing Spontaneous Adverse Event Report

BIOTECH INDUSTRY S.A.

21 Rue Bernard Haal
L 1711 Luxembourg
Tel: 00 352 26 25 94 62/63
Fax: 00 352 26 25 94 60

SPECIAL STORAGE CONDITIONS
No special storage conditions are required.
NEW FILL® powder should be stored at room temperature away from heat (maximum 30°C).
IF THE VIAL OR THE FLIP-OFF CAPSULE ARE DAMAGED, DO NOT USE.

TIPS FOR USE
1. Before all treatment with NEW FILL®, the patient should be informed completely of the indications, contra-indications, warnings, precautions for use, possible side effects and mode of administration of NEW FILL®. A complete medical history should be taken, to make sure that the treatment is appropriate.
2. Respect the rules of asepsis and hygiene. Clean the injection site with an antiseptic.
3. NEW FILL® powder should be reconstituted extemporaneously with 3 ml of water for injections, prior to subcutaneous or intradermal injection. A needle is introduced into the depressed area to be corrected; the angle of the needle depends on the depth of the depressed area and which area is to be treated.
   The needles supplied for this use have been specially designed for NEW FILL®.
4. During the first treatment session with NEW FILL®, only a limited correction should be made. The patient should then be seen later, to adjust and perfect the treatment. The patient should be informed of this at the first consultation.
5. Ice is applied to the area to be treated, immediately before the injection (in a suitable cloth, avoiding any direct contact with the skin), which considerably reduces side effects from the injection.

Manufacturer:

BIOTECH INDUSTRY S.A.

21 Rue Bernard Haal
L 1711 Luxembourg
Tel: 00 352 26 25 94 62/63
Fax: 00 352 26 25 94 60

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12.3.1 Summary of Clinical Bibliography

The first eight references listed in Section 12.3.2 discuss the use of NEW-FILL in a clinical study setting for the treatment of the signs of facial lipoatrophy. These data were presented at several different conferences within the past three years. Although the studies differ in design and objective, all studies concluded that NEW-FILL was a safe and effective product for the correction of facial lipoatrophy in HIV-seropositive patients. These studies are discussed the Clinical Sections 8.3.1 to 8.3.4 in more detail.

The article by Dr. J.N. Day *et al*, discusses a study conducted at the North Manchester General Hospital in the U.K. and gives some information on 27 patients who were treated with NEW-FILL. The article stated that all patients had an improvement in their appearance and the treatment was well tolerated with swelling and discomfort for 48 hours after treatment and one patient with a pustule not requiring specific treatment.

The article by T. Sechhi and E. Carbonnel of Lyon France discussed the use of two products available in France (NEW-FILL and Outline®) for the treatment of facial lipoatrophy. The author has used NEW-FILL in his private practice on 30 patients. Treatments were every 2 to 4 weeks with 3 to 5 injections on average. Immediate tolerance was good except for ecchymosis at the injection site. There were no immediate or delayed allergies reported. Some patients experienced subcutaneous nodules. Outline is currently being used in a compassionate protocol in a hospital where 50 patients have been treated. They required on average 3 to 8 treatment sessions. At 6 to 9 months post treatment no secondary effects have been seen. The authors conclude that the correction of lipoatrophy presents a human dimension in the face of the actual distress of the patients.

<u>Other Information</u>

Many articles discuss lipoatrophy (the loss of facial fat) and lipodystrophy. The articles include a general overview of the syndrome and possible causes and incidence of the syndrome, as well as the psychological aspect affecting those patients who have to deal with the disturbing changes to their appearance.

The Dr. Berger article, the N. Cheonis article, and the J. Berry article are from United States (US) publications written for HIV positive individuals. These articles discuss the use of NEW-FILL for facial wasting. Two articles cite the studies performed in Europe and the positive results that were reported. The articles also discuss the use of NEW-FILL in Mexico and the US. The J. Berry article is about his personal treatment experience with NEW-FILL. This patient describes the procedure, the side effects he experienced, and the effect of treatment after 4 sessions. He stated that he would do it again "in a heartbeat" and offered some tips for others to consider.

The articles note that the product is not approved for use in the US; however, some product has been imported into the US and used for patients with facial lipoatrophy. FDA "personal use guidelines" had allowed the product to be brought in for use via the Direct Access Alternative Information Resources (DAAIR) non-profit buyers club. However, this process was halted once the FDA classified NEW-FILL as a device. Currently, physicians can only legally import the

product for a limited number of patients provided that they apply for and receive and Investigational Device Exemption (IDE) from the FDA.

The Cheonis article and the Jopp article present other options and other treatments that are available for facial lipoatrophy; such as solid facial implants, injection of different alloplastic materials [(silicone, microspheres made of polymethylmethacrylate, injection of biodegradable materials (body fat cell transplants, hyaluronic acid and polylactic acid)]. Jopp presents an overview of polylactic acid and notes that it is synthetic, bioabsorbable, and biodegradable, immunologically inactive and remains *in situ*. Jopp also cites the Dr. Amard study that showed increase in skin thickness detected via sonography.

In several of the publications, especially the K. DeMott article, the authors note that the injection procedure may be an issue with NEW-FILL and care should be taken when using this product. Since this is an injectable material different from other injectable products, proper training with this device should be initiated in order to achieve the desired results. Proper administration of the product includes: several treatment sessions spaced at least 2 weeks apart, proper injection technique (depending on the site to be injected), massage of the area treated, and the use of ice post treatment. The number of sessions that are needed by a patient will vary based on the severity of the defect.

The Laglenne article discusses NEW-FILL as a new product for filling wrinkles and skin depressions. The article notes the preclinical and clinical studies carried out with this product and the safety and efficacy of the treatment. Before and after pictures are presented as well showing the treatment effects. The author concludes that NEW-FILL is simple to use, has no allergy or toxicity risk, is safe and has long-term effect of treatment (> 1 year).

Dr. Pons-Guiraud presents information on the side effects from some filling materials, including NEW-FILL. In summary she notes that the side effects due to wrinkle filling products are surely few given the number of patients treated. However, degradable products may cause transitory and reversible secondary reactions, which may be prevented by thorough, selective questioning of the patients and/or, depending on the product chosen, by tests conducted prior to treatment. Non-degradable products may cause very delayed appearance of long term or even permanent granulomas, which are a source of considerable physical and mental difficulty, not predictable by intradermal tests. For this reason, it seems preferable to use degradable products, which, despite their relatively short duration in situ, offer safety, and physical and psychological satisfaction to patients.

An article is presented from the Dermatology Clinic at Ludwig Maximilian University in Munich Germany. This is a case report of a 48 year old female patient treated with NEW-FILL in the glabellar folds and both nasolabial folds. As well, the patient received 3 additional treatments with Dysport® in the glabellar area. One year after NEW-FILL treatment the patient developed visible and palpable plaques and papules in the treated areas. Histological exam revealed a foreign-body granuloma, while electron microscopy showed remnants of the implant material. The authors conclude that poly-L-lactic acid can induce a foreign-body reaction.

Dr. Saylan from Düsseldorf, Germany, discusses several facial fillers currently unapproved for use in the US. Specifically mentioned are Hyaluronic Acid, Artecoll, DermaLive and

DermaDeep and PLA (NEW-FILL). Dr. Saylan has used all of these products and has encountered complications with all of them. He reports inflammatory local reactions, granulomas and hardening. With the use of NEW-FILL he has also seen infection, granuloma and long-term allergic reactions. Dr. Saylan concludes that in his opinion "long-term aesthetic consequences of using permanent or long-lasting facial-filling material merit careful consideration".

Based on the information provided in the listed publications, NEW-FILL is considered to be a safe and effective product for HIV-positive individuals who desire cosmetic correction for the signs of facial lipoatrophy. However, as with any injectable product there may be adverse effects seen after their use. It is important to remember that every person desiring treatment with this device, or any other, should be fully informed of the risks and benefits of the treatment and be able to make a well thought out and informed decision.

Studies of the product are ongoing for the treatment of lipoatrophy in Spain and Italy; however, these data were not available for this submission. Dermik intends to submit additional safety data from these studies as they become available in a periodic update.

12.3.2 Clinical Bibliography List of References

1. Valantin, M-A.; Aubron-Olivier, C.; Ghosn, J.; et al. "Polylactic acid implants (NEW-FILL®) in the correction of facial lipoatrophy in HIV-infected patients (VEGA study): results at 96 weeks [poster]". Presented at: 10th Conference on retroviruses and opportunistic infections; Boston, MA; February 2003.

2. Valantin, M-A.; Aubron-Olivier, C.; Ghosn, J.; et al. "Polylactic acid implants (NEW-FILL®) to correct facial lipoatrophy in HIV-infected patients: results of the open-label study VEGA," AIDS, November 2003, 17:2471–2477.

3. Boix, V. "Polylactic acid implants. A new smile for lipoatrophic faces?" AIDS, 2003, v17, n17, p2533-2535.

4. Moyle, G.J.; Lysakova, L.; Brown, S.; et al. "A randomised open label study of immediate versus delayed polylactic acid injection in persons with HIV [abstract]." Presented at: 42nd Interscience Conference on Antibiotic Agents and Chemotherapy; San Diego, CA; October 2002.

5. Amard, P.; Saint-Marc, T.; Katz, P. "The effects of polylactic acid (PLA) (NEW-FILL®) as therapy for lipoatrophy of the face [abstract]". Presented at: 2nd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV; Toronto, Ontario; September 13-15, 2000.

6. Lafaurie, M.; Dolivo, M.; Boulu, D.; et al. "Treatment of facial lipoatrophy with injections of polylactic acid in HIV-infected patients [poster]". Presented at: 10th Conference on retroviruses and opportunistic infections; Boston, MA; February 2003.

7. Engelhard, P. and M. Kines. "Safety and Efficacy of NEW-FILL® (Polylactic Acid) in the Treatment of HIV-associated Lipoatrophy of the Face (HALF): [abstract]". Presented at: XIV International AIDS Conference; Barcelona, Spain; July 2002.

8. Day, J.N.; Raabe, A.; Shiner, A.M.; Wilkins, E.L. "Intradermal polylactic acid (Newfill) for treatment of severe HIV-associated facial lipoatrophy," HIV Medicine, 2002, 3(3):162.

9. Sechhi, T. and Carbonnel, E. "Outpatient correction of lipoatrophies of the face in HIV infection using the filling technique" (Correction ambulatoire des lipo-atrophies du visage dans l'infection à VIH par technique de comblement). Nouvelles Dermatologie. 2003, v22, p132-133.

10. Berger, D.S. "New facial filling treatment for lipodystrophy," Positively Aware, 2001, v12, n5, p17-20.

11. Cheonis, N. "NEW-FILL to treat facial wasting," Bulletin of Experimental Treatments for AIDS, 2002, v15, n2, p10-15.

12. Berry, J. "NEW-FILL for an old face". Positively Aware, 2002, v13, n3, p34-35.

13. Jopp, A. "Therapeutic options in facial lipoatrophy caused by HAART," AIDS and HIV Infections, 2001, v17, n2, p1-6.

14. DeMott, K. "NEW-FILL: Difficult to use, but gives lasting results," Skin and Allergy News, August 2002, p40.

15. Laglenne, S.; Lalanne, B.; Laglenne, B. and Asius, J. "A new, totally resorbable wrinkle-filling product" (Un nouveau produit de comblement des rides, entièrement resorbable). Nouvelles Dermatologie. May 2000, V54, p30-33.

16. Pons-Guiraud, A. "Update on the side effects of wrinkle-filling products" (Actualisation des effets secondaires des produits de comblement des rides). Nouvelles Dermatologie, 2003, v22, p205-210.

17. Oppel, T.; Schaller, M.; Flaig, M. and Korting, H.C. "Facial foreign body granulomas after dermal injection of a polylactate-based preparation for wrinkles" (Fremdköpergranulome nach dermaler injection eines auf poly-milchsäure basierenden implantates zur behandlung von falten). JDDG, 2003, v1, p220-222.

18. Saylan, Z. "Facial fillers and their complications", Aesthetic Surgery Journal, May/June 2003, v23, n3, p221-224.

12.3.3 Clinical Bibliography Referenced Articles

Volume - Page Number

1. Valantin, M-A.; Aubron-Olivier, C.; Ghosn, J.; et al. "Polylactic acid implants (NEW-FILL®) in the correction of facial lipoatrophy in HIV-infected patients (VEGA study): results at 96 weeks [poster]". Presented at: 10th Conference on retroviruses and opportunistic infections; Boston, MA; February 2003.
    13-275

2. Valantin, M-A.; Aubron-Olivier, C.; Ghosn, J.; et al. "Polylactic acid implants (NEW-FILL®) to correct facial lipoatrophy in HIV-infected patients: results of the open-label study VEGA," AIDS, November 2003, 17:2471–2477.
    13-282

3. Boix, V. "Polylactic acid implants. A new smile for lipoatrophic faces?" AIDS, 2003, v17, n17, p2533-2535.
    13-290

4. Moyle, G.J.; Lysakova, L.; Brown, S.; et al. "A randomised open label study of immediate versus delayed polylactic acid injection in persons with HIV [abstract]." Presented at: 42nd Interscience Conference on Antibiotic Agents and Chemotherapy; San Diego, CA; October 2002.
    13-294

5. Amard, P.; Saint-Marc, T.; Katz, P. "The effects of polylactic acid (PLA) (NEW-FILL®) as therapy for lipoatrophy of the face [abstract]". Presented at: 2nd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV; Toronto, Ontario; September 13-15, 2000.
    13-299

6. Lafaurie, M.; Dolivo, M.; Boulu, D.; et al. "Treatment of facial lipoatrophy with injections of polylactic acid in HIV-infected patients [poster]". Presented at: 10th Conference on retroviruses and opportunistic infections; Boston, MA; February 2003.
    13-304

7. Engelhard, P. and M. Kines. "Safety and Efficacy of NEW-FILL® (Polylactic Acid) in the Treatment of HIV-associated Lipoatrophy of the Face (HALF): [abstract]". Presented at: XIV International AIDS Conference; Barcelona, Spain; July 2002.
    13-310

8. Day, J.N.; Raabe, A.; Shiner, A.M.; Wilkins, E.L. "Intradermal polylactic acid (Newfill) for treatment of severe HIV-associated facial lipoatrophy," HIV Medicine, 2002, 3(3):162.
    13-315

9. Sechhi, T. and Carbonnel, E. "Outpatient correction of lipoatrophies of the face in HIV infection using the filling technique" (Correction ambulatoire des lipo-atrophies du visage dans l'infection à VIH par technique de comblement). Nouvelles Dermatologie. 2003, v22, p.132-133.   13-317

10. Berger, D.S. "New facial filling treatment for lipodystrophy," Positively Aware, 2001, v12, n5, p17-20.   13-322

11. Cheonis, N. "NEW-FILL to treat facial wasting," Bulletin of Experimental Treatments for AIDS, 2002, v15, n2, p10-15.   13-327

12. Berry, J. "NEW-FILL for an old face". Positively Aware, 2002, v13, n3, p34-35.   13-334

13. Jopp, A. "Therapeutic options in facial lipoatrophy caused by HAART," AIDS and HIV Infections, 2001, v17, n2, p1-6.   13-337

14. DeMott, K. "NEW-FILL: Difficult to use, but gives lasting results," Skin and Allergy News, August 2002, p40.   13-345

15. Laglenne, S.; Lalanne, B.; Laglenne, B. and Asius, J. "A new, totally resorbable wrinkle-filling product" (Un nouveau produit de comblement des rides, entièrement resorbable). Nouvelles Dermatologie. May 2000, V54, p30-33.   13-347

16. Pons-Guiraud, A. "Update on the side effects of wrinkle-filling products" (Actualisation des effets secondaires des produits de comblement des rides). Nouvelles Dermatologie, 2003, v22, p205-210.   13-354

17. Oppel, T.; Schaller, M.; Flaig, M. and Korting, H.C. "Facial foreign body granulomas after dermal injection of a polylactate-based preparation for wrinkles" (Fremdköpergranulome nach dermaler injection eines auf poly-milchsäure basierenden implantates zur behandlung von falten). JDDG, 2003, v1, p220-222.   13-368

18. Saylan, Z. "Facial fillers and their complications", Aesthetic Surgery Journal, May/June 2003, v23, n3, p221-224.   13-375